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LEPRECHAUNISM

BY

PHILIP RAINSFORD EVANS

From The Hospital for Sick Children, Great Ormond Street, and Guy's Hospital, London

(RECEIVED FOR PUBLICATION JUNE 12, 1955)

'Are you going to listen to what I am telling you about the Leprecaun?' said the Thin Woman in James Stephens's *The Crock of Gold*. 'I am not', said the Philosopher, and the description by Donohue (1948) of a case of 'dysendocrinism' seems to have received as little notice. Now he and Uchida (1954) have redescribed the patient and given an account of her sister (who was similarly affected) under the title of 'Leprechaunism'.

Their patients were daughters of consanguineous parents. The children's growth appeared to be halted at about the seventh month of pregnancy; the elfin facies suggested the name; both children died and at necropsy showed evidence of endocrine disturbance in the ovaries, pancreas, breasts and clitoris, as well as deposition of glycogen and iron in the liver and calcium in the kidneys.

When the description of the Toronto cases appeared, two children were seen in London who had some of the same characteristics. In one, an older child, large ears and congenital mammary hypertrophy suggested the diagnosis; in the other, the general resemblance of the baby to that illustrated in Donohue and Uchida's Fig. 1 operated similarly. In neither case was the identity complete, for in each some of the abnormalities of the Canadian infants were lacking.

Case Reports

Case 1. This girl was the third child of healthy Jewish parents not related by blood; the elder sister and brother were also well. Pregnancy and delivery were normal; the birth weight was 6¾ lb. The baby was always difficult to feed, for she would not suck for long, although she did not appear tired. Breast feeding was abandoned at the end of the first week, but bottle feeding was no better. At the age of 12 weeks she weighed only 7¼ lb., so she was admitted to the Victoria Hospital, Blackpool, under Dr. Gordon Hesling. Detailed investigations showed no reason for her failure to thrive and even when alternate feeds were given by oesophageal tube she did not gain weight. At 16 weeks Dr. Hesling referred her to Dr. Reginald Lightwood who admitted her to The Hospital for Sick Children, Great Ormond Street, London.

She was seen to be (Fig. 1) a small, thin, fretful baby who cried lustily. Her cheeks were sunken, chin pointed, eyes wide apart and showing very dark irides, nose negroid and ears set low on the head (Fig. 2). The head measured 15¼ inches in circumference, the anterior fontanelle was wide, the posterior fontanelle was closed. The hands and feet were large, and the skin creases showed brown pigmentation. The nipples and areolae were large and protuberant; the clitoris was enlarged (Fig. 3). Moro and grasp reflexes were present. There was a rough systolic praecordial murmur; the blood pressure was 95/65 mm. Hg.

Various diagnoses had been considered and found to

FIG. 1.—Case 1: Emaciation and prominence of nipples (age 4 months).

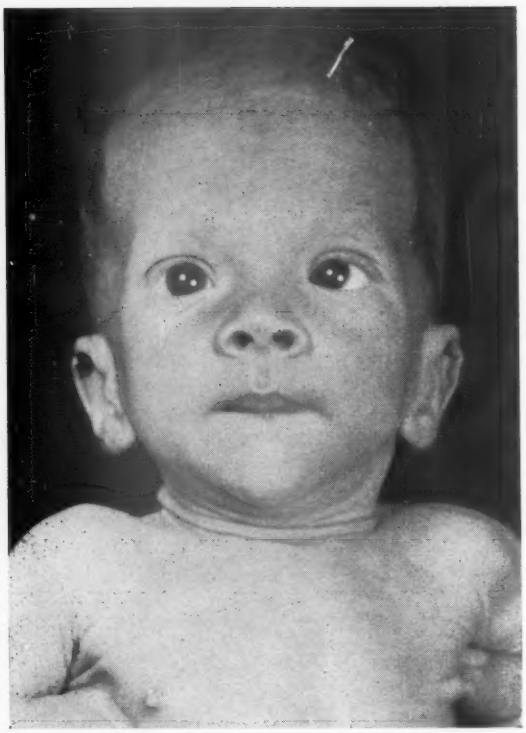

FIG. 2.—Case 1: High forehead, wasting of face, wide eyes, pointed chin, low ears (age 4 months).

be untenable when the paper by Donohue and Uchida (1954) appeared and the resemblance between our patient and theirs was noticed; the hyperplasia of nipples and clitoris reinforced the impression that this infant might be an example of leprechaunism.

Between the ages of 3 and 8 months results of the following investigations were normal: blood values for urea, calcium, sodium, potassium, bicarbonate (all done twice); chloride, galactose, Wassermann reaction, toxoplasma, complement-fixation and Sabin-Feldman dye tests, and amino-acids; urinary amino-acids (twice) and sugars by chromatography, blood counts and sedimentation rate, leucocyte sex chromatin, tryptic activity of faeces (twice), serum antithrombin titre, electrocardiogram, radiographs of chest, heart and oesophagus (barium swallow).

The urine occasionally contained a trace of albumin, but was otherwise normal (no phenylpyruvic acid); the total plasma proteins were 5·7 g. % with some increase in α_2, β and γ globulins.

The growth failure was associated with a decrease in bone development: the bone age at 4 months was up to the standard of girls of 1½ months, and at 8 months it had reached the standard for 3 months. Pituitary hypofunction was suspected as the cause. Radiography of the skull showed a normal pituitary fossa; air encephalography revealed normal third and fourth ventricles, a normal aqueduct, but some evidence of atrophy of the right cerebral hemisphere as the right lateral ventricle was larger than the left, and there was possibly some widening of the sulci over this hemisphere. Cerebrospinal fluid was examined twice and was normal except that on one occasion the sugar content was low, 34 mg. %. Similarly, the fasting blood sugar was occasionally rather low; on different occasions the figures were 110, 70, 78, 55, 62 and 56 mg. %; by paper chromatography the blood glucose was estimated to be 37 ± 2 mg. %. Blood glycogen was normal or low, 6·8 mg. %. A glucose tolerance test was normal, and so were the glucose and the eosinophil responses to the injection of adrenalin, but the response to insulin was abnormal, showing an excessive, and more especially a prolonged, fall in blood sugar.

The urinary excretion of follicle-stimulating hormone was less than 5 mouse units in 24 hours, i.e., not excessive; a vaginal smear showed no evidence of oestrinization, the excretion of 17-ketosteroids was 0·6 mg. and 0·43 mg./24 hours (normally not over 0·1 mg., Talbot, Butler, Berman, Rodriguez and MacLachlan, 1943). Laparotomy showed that the liver and spleen were slightly enlarged and the ovaries were cystic, but no microscopic abnormality was found in small biopsy specimens of liver, ovary or pancreas.

The infant was kept in hospital from the age of 4 months to 9 months. During this time she made slow progress. The head increased in circumference by 1¼ in. (16½ in. at 9 months), weight increased from 8¼ lb. to 10½ lb., length from 22¼ in. to 23½ in. The cardiac murmur became almost inaudible. Cortisone (14 g. by mouth in one month) appeared not to affect her progress. On discharge at 9 months she seemed to have reached

FIG. 3.—Case 1: Wasting, enlargement of clitoris (age 4 months).

a 5-month level in some motor activities, but she had very little control of her back, although head control was good.

This child resembled the patients of Donohue and Uchida in external appearance, enlargement of nipples, areolae and clitoris, defective growth, and cystic changes in the ovaries. By contrast the ears were not particularly large, pregnancy and weight at birth were normal, there was no facial hirsuties, and no histological changes were found in liver or pancreas. The slow growth, delayed ossification and hypersensitivity to insulin suggested that there was a deficient production of growth hormone by the pituitary.

Case 2. This girl was referred to Guy's Hospital when she was 2¾ years old. I thought she was simply mentally retarded and noted the associated congenital anomalies of enlargement of the ears and mammae. Two days later I read Donohue and Uchida's account of leprechaunism, and then arranged for her to be admitted to hospital for investigation.

She was the third child of healthy parents who were not related by blood; her two older and one younger brothers were well. Pregnancy and birth were normal, when she weighed 7 lb. She was easy to feed and enjoyed good health except for eczema, which started at 9 months and was not severe. She developed slowly; sat at 1 year, stood at 1½ years and walked alone at 2½ years. She fed herself with her hands but could not use a spoon and used only two words with meaning. She was thin, weighing 26 lb. (average for 2 years), height 36 in. (average for her age), head circumference 18 in. (average for 1 year), span 36½ in. (average for 3½ years). She was a blue-eyed, fair-haired child, with a vapid expression and rather wide eyes, but her facies did not much resemble that of the leprechaun babies. The ears were large and rather bat-like (Fig. 4). Mammary enlargement had been noticed at birth, but was thought to be diminishing gradually. The areola was chiefly involved (Fig. 5) and the tissue under it felt like mammary tissue, not fat. The clitoris was not enlarged. There was slight contracture which prevented either ring finger from being fully extended; the second toe on the left foot was permanently slightly dorsiflexed; there was a dimple over the sacrococcygeal junction, slightly to the right side.

FIG. 4.—Case 2: Wide eyes, large ears (age 2¾ years).

FIG. 5.—Case 2: Prominence of mammary areola (age 2¾ years).

The liver was palpable two fingerbreadths below the costal margin. The blood pressure was 95/65 mm. Hg. She was slightly anaemic: Hb 66% (10·2 g. %), white blood count normal; the blood calcium, phosphate, alkaline phosphatase, sodium, potassium, chloride and protein (albumin and total globulin) were normal. The blood urea was 41 mg., plasma bicarbonate 34·7 vol., and blood glycogen 13·4 mg. % (normal). Urinary gonadotrophins were not increased (negative to 12 mouse units in a 24-hour specimen), but 17-ketosteroids were slightly raised: 3 mg. and 2·4 mg. in 24-hour specimens (normally not over 0·4 mg. according to Talbot *et al.*, 1943). A vaginal smear showed a few squames with slight reddish staining indicating the presence of glycogen. Radiographs of the whole skeleton showed no abnormality except a bone age of 1-1½ years; air encephalography showed (as in Case 1) some dilatation of the right lateral ventricle. The glucose tolerance curve was rather high; injection of adrenalin also was followed by

a considerable rise of blood sugar from 62 to 134 mg. % in 45 minutes. The injection of insulin was followed (as in Case 1) by an unusually prolonged fall in blood sugar.

Laparotomy showed slight enlargement of the liver; the spleen was about twice the normal size, the ovaries were enlarged and cystic measuring on the right side $1\frac{1}{2} \times \frac{3}{4} \times \frac{1}{2}$ in. The kidneys and pancreas appeared normal. The biopsy specimen of the pancreas was normal; in the liver there was no increase in iron but there was moderate diffuse glycogen infiltration, predominantly centrilobular, and chemical assay showed 1·58 g. % (normal 0·4%).

Methyltestosterone, 5 mg. in propylene glycol, was given daily by mouth for eight weeks. During this time weight increased by only 2 lb. and height perhaps not at all (it was difficult to measure accurately), but the mammary enlargement seemed a little less. The bones and epiphyses in the limbs had increased in size, but there were no new carpal centres. There was no significant change in excretion of urinary gonadotropins or 17-ketosteroids (2 mg./24 hr.); blood urea was normal (29 mg. %); a vaginal smear showed faint staining for glycogen; after insulin injection there was still some delay in restitution of the blood sugar level, but the fall was not as great as before. One month later (after no further testosterone had been given) the weight had increased by $2\frac{1}{2}$ lb. and the nodular feeling of the mammary tissue was no longer detectable.

This child resembled the cases of Donohue and Uchida in having large ears, congenital mammary enlargement, increased liver glycogen, large cystic ovaries and decreased bone age. By contrast, pregnancy, birth weight and feeding were normal and the clitoris was not large. The facial appearance was not characteristic, but she was much older than the other patients. She also had increased response to insulin and slightly increased 17-ketosteroid excretion.

Discussion

For practical purposes it suffices to define a leprechaun as 'In Irish folk-lore, a pigmy sprite' (*Shorter Oxford English Dictionary*). Something more detailed is needed for the definition of leprechaunism, but as yet too few cases have been described to enable one to list the essential and the concomitant features. One cannot even answer the important and perhaps critical question, Are there males with leprechaunism?

Some failure of growth, including delay in ossification; a characteristic facies in infancy, usually with large ears, wide eyes and hollow cheeks; congenital enlargement of mammary ducts, areolae and nipples; enlargement of liver and ovaries, with an unusually great number of follicular cysts in the latter; all these seem to be important features. In addition, the clitoris and labia minora may be large, and so may the kidneys and spleen. Mental defect is probably one of the major features, but only one of the four patients has been seen at an age when this is certain.

Further study of carbohydrate metabolism is likely to help. In the two babies examined at necropsy, there was hyperplasia of the islets of Langerhans and in one the insulin content of the pancreas was found to be much increased. In three of the four children the liver contained excessive glycogen, but it was (in the two surviving patients) easily mobilized by adrenalin; their reaction to insulin was excessive.

We can imagine that these children resemble those suffering from Turner's syndrome in that they are born with certain anatomical abnormalities—in this case the characteristic facies, large ears and perhaps mental defect—but that some of their other peculiarities are secondary to a developmental anomaly of an endocrine gland. Some of the effects may well be secondary to pituitary deficiency: delay in bone growth, failure to respond to hypoglycaemia induced by insulin, and the wasting seen in the three babies, point in this direction. Pituitary deficiency alone would, however, be unlikely to cause mammary and clitoridean enlargement, or a slight increase in excretion of 17-ketosteroids—rather, the reverse.

In discussing this difficulty with Dr. Douglas Hubble, he suggested that overproduction of oestrogens should be considered. The ovaries were reported to be cystic in all four cases and were certainly enlarged in three. This enlargement might be assumed to occur in foetal life independently of the pituitary and it might be associated with increased production of oestrogens. This would explain the enlargement of nipples, areolae and mammary ducts. The evidence of experiments in animals has been well summarized by Burrows (1949). Oestrogens inhibit the production of pituitary growth hormone in the rat (Reece and Leonard, 1939; Gaarenstroom and Levie, 1939; Griffiths and Young, 1942), increase insulin production by the pancreas (Griffiths and Young, 1940), which is a possible cause of the failure to respond to hyperglycaemia induced by the injection of insulin, and produce hypertrophy of labia minora (Lewis, 1933). The enlargement of the clitoris seen in three cases was not as great as in adrenal hyperplasia and is perhaps analogous to the enlargement which occurs at puberty. Hypercalcaemia was not demonstrated in our patients, but the kidneys were calcified in the Canadian cases, and it is interesting to recall that oestrogen administration has been found to cause a rise in serum calcium in mice (Wentworth, Smith and Gardner, 1940).

This unsure hypothesis may be summarized by suggesting that in leprechaunism there are congenital (probably genetic) abnormalities of the face, ears and ovaries; that the ovaries may produce oestrogen in excess and that this may cause: (1) slight hyperplasia of nipples, areolae, mammary ducts, clitoris and labia minora, with slight increase of 17-ketosteroid excretion (prepubertal changes); (2) decrease of pituitary growth hormone which causes wasting of the soft tissues and delay in the growth of bones, as well as increased insulin production, and lack of response to hypoglycaemia (metabolic disturbances).

This hypothesis indicates the need for assay of oestrogens (which we were unable to carry out) in such cases, and for discovering whether an analogous condition occurs in the male.

Androgens inhibit oestrogens so treatment with male hormones could be tried. As yet nothing impressive has come out of such a trial in these two patients.

Summary

In 1954 Donohue and Uchida described two sisters with a characteristic facies, large ears, hyperplasia of mammary ducts, clitoris and ovaries, failure to grow, and increased glycogen in the liver and insulin in the pancreas. Two children thought to belong to the same group are described here.

These children, it is suggested, may perhaps combine anomalies of anatomical development with abnormalities caused by ovarian hypersecretion starting in foetal life.

My thanks are due to my colleagues, too numerous to mention individually, who have helped to investigate these patients.

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PALPABLE CONTRACTILE PYLORIC TUMOURS IN THE NEWLY BORN

BY

W. S. CRAIG

From the Department of Paediatrics and Child Health, the University of Leeds

(RECEIVED FOR PUBLICATION AUGUST 19, 1955)

A palpable tumour which contracts and relaxes is generally accepted as conclusive confirmatory evidence of symptoms and signs suggestive of hypertrophic pyloric stenosis in infancy. The writer's experience, in common with that of other workers, is that a contractile tumour is present in 98% of infants with pyloric stenosis examined for the first time over the age of 2 weeks. A detailed study carried out over the past two and a half years suggests that the same significance cannot invariably be attached to the palpation of a contractile pyloric tumour in babies under 2 weeks of age. The purpose of this article is to describe the findings which have given rise to these doubts.

The term 'tumour' is used throughout as meaning a clinically detectable swelling.

Origin of the Study

The study began as a result of the unexpected finding of a contractile pyloric tumour in a baby girl aged 7 days, reported on account of a tendency to recurrent regurgitation and unsatisfactory weight progress from the third day of life. There were no obvious factors arising in the mother or infant to account for the baby's symptoms which were disconcerting rather than alarming. Regurgitation gradually lessened and eventually ceased with regular daily stomach lavages and without any modification of the feeding routine. A large quantity of mucus was present in the early lavages. Discharged from hospital on the fourteenth day of life, the infant was examined at intervals for a further period of two months. The tumour became less readily palpable at successive examinations, and was no longer detectable two months after the baby had been discharged from hospital. Progress during these two months was symptomless and uneventful.

By what can only be described as sheer coincidence a pyloric tumour was palpated in similar circumstances in another baby within a few weeks of the one described.

Choice of Clinical Material

In view of the above accidental findings it was decided to carry out organized clinical studies on two series of cases, viz.:

A. Infants of less than 14 days of age in whom an unsatisfactory weight progress was associated with pronounced posseting, regurgitation or/and vomiting over a period of more than 48 hours. (Babies with symptoms which might have been contributed to by nasal catarrh, swallowing air, abnormalities of the palate or mandibular joint, or by difficulties related to the mother's nipples and breasts were excluded. No baby with fever, detectable infection or enteritis was included. Constipation was not a feature in any case.)

Twenty-one babies are included in this series. Of them, 18 were born in Leeds Maternity Hospital. Two were admitted to the hospital from their homes and one from a nursing home. Premature babies are not included.

B. A control series consisted of 115 healthy newborn infants who showed uninterrupted progress, and who did not experience any feeding difficulties. All the infants were born at term in the Leeds Maternity Hospital. Their ages at the time of examination ranged from 5 to 7 days. In other respects the babies were unselected, no account being taken of sex, place in family or the method of feeding.

Method of Examination in Hospital

The same procedure was adopted for all infants in series A and B. After lavage of the baby's stomach, abdominal examination was carried out while the baby was being fed. Palpation was begun immediately before the start of a feed, interrupted occasionally to allow the infant to 'break wind', and continued for some little time after completion of the feed. Feeding during the time of examination was invariably by bottle. This procedure was adopted to facilitate examination. The milk given was human or cow's according to that which the baby had been receiving as a routine in the lying-in

ward. The results of gastric lavage were noted in every case. All babies were examined and the results recorded independently by a second competent observer.

Methods of Follow-up

As indicated below, contractile pyloric tumours were palpated in the majority of infants included in the first series A, and in a proportion of those included in the control series B. Babies in whom a tumour was palpated were re-examined by the writer at intervals extending over a number of weeks or months until such time as the tumour could no longer be felt. In most instances the infant was brought to hospital for re-examination, in which event the procedure followed was similar to that already described. Infants living at a considerable distance from the hospital were visited personally in their homes and examined at the baby's customary feeding time, but preliminary gastric lavage was not practicable.

Infants in whom no tumour was palpated during the time they were in the Maternity Hospital were not followed up personally. They were, however, the subject of follow-up visits by health visitors in the employ of the City of Leeds Maternity and Child Welfare Department.

Observations concerning the Presence or Absence of a Tumour

Examination of the abdomen after gastric lavage facilitates palpation of individual intra-abdominal structures. It is possible to palpate the pylorus in a large number of newborn infants. Palpation throughout the time of a feed facilitates detection of changes in the pylorus which accompany the gradual filling of the stomach.

In a small number of infants the pylorus could not be felt at any time—before, during or after a feed. In others it was recognizable as a short ribbon-like or worm-like structure subject to changes in firmness or tone. Not infrequently a vague sense of soft thickening was felt at intervals at a point in the length of the pylorus. Less frequently but not rarely, the local thickening was characterized by greater firmness and by a fusiform or spheroidal shape. Pyloric thickening in its most unmistakable form was characterized by a combination of precise definition and pronounced firmness. Exceptionally the firmness assumed a degree of extreme hardness.

The shape of the thickening varied. In some it was round or spheroidal; in others it resembled that of a spinning top. 'Hardening' only became detectable after the start of feeding. Evidence of defined shape and contraction usually appeared after approximately 1 oz. of feed had been taken. Local thickening and hardening, when present, were not persistent. They tended to appear and disappear.

For the purpose of the study a tumour has been regarded as being present if the palpable pyloric thickening (*a*) had definition, whether spherical or 'spinning top' in shape, (*b*) had an appreciably firm or distinctly hard consistence, (*c*) was felt to contract and relax repeatedly, (*d*) was felt on each occasion at the time of successive examinations and (*e*) was felt by more than one competent observer.

Infants in whom all these five conditions were not satisfied were not included among those with tumours. This involved the exclusion of all borderline cases.

Importance was not attached to the apparent size of the tumour. The fact that definition, consistence and contraction were detectable was accepted as having greater significance than size, more especially as in older infants with pyloric stenosis clinical impressions concerning the size of the tumour are frequently not borne out at operation.

Clinical Findings

A: Selected Series (21 Infants). Of the 21 infants constituting this series, 11 were males and 10 females. There were 11 first-born babies. The place in the family of the remainder was as follows: second, seven babies; fourth, one; fifth, one; and eleventh, one baby.

A tumour was palpated in 17 of the series. An indefinite localized thickening was felt in two, and the findings were completely negative on examination of two other babies. Peristalsis was seen in all infants in whom a tumour was felt, and in two of those in whom no tumour was detected. A feature of all 21 infants was the large amount of viscid mucus in the gastric lavage.

Three male infants (two first-born and one a second child) were referred to a surgical colleague. In each case operation resulted in the immediate relief of symptoms, the severity and persistence of which had indicated the need for surgical intervention (Fig. 1). Management of the other 18

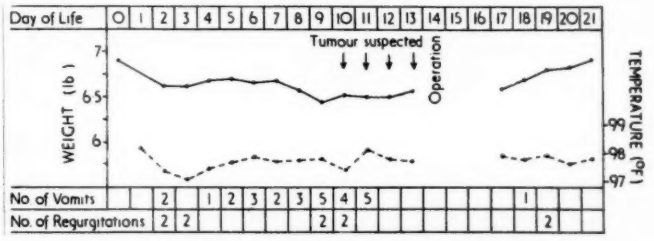

FIG. 1.—Chart of Baby 3, Series A (see Appendix).

infants was limited to gastric lavage. Symptoms subsided within seven to 14 days of onset. All 21 infants were followed up for a period of not less than six months. In no instance was there a return of symptoms. The tumours which were felt in 14 infants, but which were not treated surgically, continued to be palpable after discharge from hospital for a period of time varying from four weeks to three months (Fig. 2).

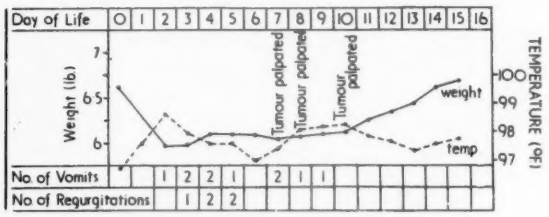

FIG. 2.—Chart of Baby 7, Series A.

Fourth child, female, normal delivery following medical induction for maternal pre-eclampsia. Hard spheroidal contractile tumour of moderate size palpable for 10 weeks. Bottle-fed on pooled human milk for five days, thereafter on dried cow's milk. No operation.

B: Control Series (115 Infants). Infants included in this series were all born in hospital and were under clinical supervision from the time of birth. There were 69 first-born babies, of whom 39 were males and 30 females. Of the 46 infants who were not first-born, 29 were males and 17 females.

In the total control series of 115 babies a tumour was felt in 16 males (including 13 first-born) and nine females (including five first-born). Mucus in large amounts was a feature of the gastric lavage in 19 of these 25 babies. Of the infants in whom a tumour was felt, 21 were followed up for a period of not less than six months. In 10 of them a tumour was no longer palpable six weeks after discharge from hospital and in the remaining 11 the tumour had disappeared by the age of 3 months.

No tumour was palpable in 90 babies in the series. Large amounts of mucus were a feature of the gastric lavage in only five of these infants. Trace was lost of three babies. One infant (a male and a first child) developed symptoms of pyloric stenosis at the age of 4 weeks and was operated upon at the age of 4½ weeks. Not one of the remaining 86 babies had symptoms attributable to primary gastro-intestinal dysfunction in the first six months of life.

Peristalsis of varying degree was seen in 15 infants in whom a tumour was detected and in 40 in whom no tumour was felt. Peristalsis was most pronounced in babies whose gastric lavage contained notably large amounts of mucus.

One of the infants with no tumour in the control series (B), was the twin sister of a male (eleventh) child who was included in the first series (A) and in whom a tumour was readily palpable.

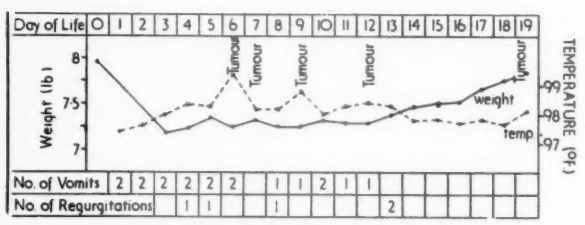

FIG. 3.—Baby 15, Series A.

Second child, female, prolonged labour, instrumental delivery, no clinical signs of intracranial irritation. Firm, fusiform contractile tumour palpable until the age of 4 months. Breast fed throughout, no operation.

Supplementary Studies

X-ray Screening (62 Infants). Sixty-two babies were screened after being given a barium feed. Screening was carried out as a routine at 3 p.m., the infant's last previous feed having been given at 9 a.m. on the same day. The 62 babies consisted of 16 (including the three who were operated on) in Series A and 46 in Series B. At the time of screening the radiologist had no knowledge of the clinical findings in the infants referred to him. Included in the 62 babies were 25 (12 from Series A and 13 from Series B) in whom a contractile

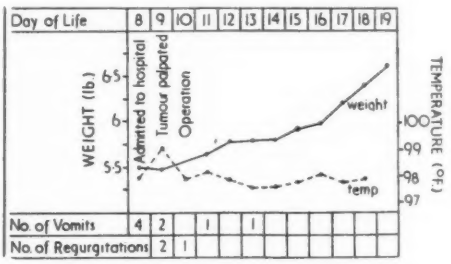

FIG. 4.—Baby 18, Series A (see Appendix).

First child, male, uneventful labour and delivery, birth weight 7 lb. Notably large, hard, contractile tumour palpated; gross gastric distension and marked peristalsis. No tumour found at operation. Cessation of symptoms after Rammstedt incision.

pyloric tumour had been palpated; 29 (all from Series B) in whom no tumour had been felt; and eight (one from Series A and seven from Series B) in whom tumours had been felt, but which because they did not satisfy the conditions enumerated on page 485 were excluded as border-line cases.

The reported findings on screening can best be summarized as follows:

IN INFANTS (29) IN WHOM NO TUMOUR WAS FELT. In 23, nothing abnormal was noted; in four, there was initial lack or slowness of peristaltic activity for

a period varying from two to 10 minutes; and in two infants, rapid emptying in association with vigorous peristalsis, was a feature.

IN INFANTS (8) IN WHOM a 'BORDER-LINE' TUMOUR WAS FELT. In five, immediate vigorous peristalsis and rapid emptying of the stomach were noted; in two, initial peristalsis was slow to appear and emptying of the stomach did not begin for a few minutes; and in one infant, peristaltic activity and emptying of the stomach were normal.

IN INFANTS (25) IN WHOM A CONTRACTILE TUMOUR WAS PALPATED. In five, nothing abnormal was noted; and in six there was initial delay in peristaltic activity and emptying of the stomach (with slight lengthening of the pyloric canal in two) and considerable delay in one. In 11 other infants, there were noted immediate markedly vigorous peristaltic contractions, notably rapid emptying of the stomach and wide dilatation of the pyloric canal—the emptying in two instances being reported on as 'amazingly rapid'.

The three remaining cases in this group consisted of those submitted to operation. In the two in whom a tumour was subsequently confirmed at operation (Appendix: Baby 3, Series A and Baby 9, Series A) screening showed gross delay in emptying of the stomach with associated distension, but appreciable amounts of barium entered the duodenum within an hour. There were no comments concerning the pyloric antra or pyloric canals. In the third infant in whom no tumour was found at operation (Appendix: Baby 18, Series A) gastric distension was gross and the barium did not begin to leave the stomach for 20 minutes, after which its passage was uninterrupted but markedly slow.

Infants Developing Symptoms of Hypertrophic Pyloric Stenosis after the Age of 2 Weeks. During the period January, 1947, to December, 1954, 23 babies were admitted to general hospitals in Leeds who were (i) born in Leeds Maternity Hospital, (ii) diagnosed at varying times after discharge from that hospital as suffering from hypertrophic pyloric stenosis and (iii) successfully operated on in a Leeds hospital. The routine clinical neonatal records kept during the time these 23 infants were under observation in the Maternity Hospital have been reviewed.

The ages of the 23 babies at the time of discharge from the Maternity Hospital ranged from 10 to 12 days. Histories taken at the time the babies were admitted to general hospitals for operation indicated that symptoms of pyloric stenosis first appeared in four infants after the age of 28 days; in five infants in the fourth week; and in 10 infants in the third week of life. Clinical records made in the Maternity Hospital of these 19 babies revealed that in every case the neonatal progress had been entirely uneventful.

In the remaining four babies the onset of symptoms of gastric obstruction occurred on the fourteenth day of life in two cases and on the thirteenth day in the other two cases. Two of these infants (both breast fed) showed unsatisfactory weight progress. In one of these cases there were no symptoms and in the other there was occasional vomiting which was neither copious nor forceful.

The four infants who developed signs of pyloric obstruction within a few days of discharge were born before the present investigation had begun and were not examined in the Maternity Hospital for the presence of a palpable tumour.

Pathological Examination of Pyloric Musculature of Newly Born Infants Dying from Whatever Cause. The pyloric musculature of 30 newly born babies born in the Leeds Maternity Hospital at differing periods of gestation and dying within 10 days of birth from a variety of causes was examined pathologically. The examinations were carried out by Dr. A. R. Macgregor, of the Royal Hospital for Sick Children, Edinburgh, and included microscopical studies. During the same period Dr. Macgregor carried out similar studies on babies who died in maternity hospitals in Edinburgh. This series consisted of 45 stillborn and 63 liveborn infants.

Macroscopically recognizable thickening in the region of the pylorus was noted in one baby and was shown microscopically to be due to the presence of clusters of heterotopic pancreatic cells. No abnormal macroscopical or microscopical features were found in the pyloric musculature of any of the remaining 137 infants.

Discussion

Comparing them with those encountered in older infants referred for operation on account of hypertrophic pyloric stenosis, the tumours (with six exceptions) palpated in the present investigation, lacked conclusiveness in one or other of their characteristics. In this respect the findings resemble in general terms those reported by Wood and Astley (1952) in cases described as 'Pseudo-pyloric Stenosis'. Whereas, however, the average age of onset of vomiting in their cases was 3 weeks, vomiting (or regurgitation) began in the first week of life in all the infants included in Series A of the present study. While all tumours in the present study were defined, some lacked precise definition.

All were firm in consistence, but the firmness conveyed a sense of hard solidity in only a small minority. The tumours tended to acquire increased definition and firmness as successive rhythmic contractions accompanied gradual filling of the stomach in the way characteristic of tumours in older infants with hypertrophic pyloric stenosis. Contraction and relaxation of the tumours in this investigation were, however, more deliberate and more sluggish. The sudden contraction and sudden relaxation suggestive of violent seizure and release commonly appreciated towards the end of a feed in the older infant with classical pyloric stenosis were present in only five cases in the present investigation. The tumour of pyloric stenosis, which becomes extremely hard with almost violent suddenness, often acquires a 'spinning top' shape with a notably sharp circumferential edge. In the present investigation these characteristics were met with in only five infants.

The Nature of the Tumour. What was the nature of the contractile tumour palpated in 25 symptomless cases (Series B) and in 17 cases (Series A) with unsatisfactory weight progress associated with recurrent posseting, regurgitation or vomiting? There were no fatal cases in either series and no material was available for pathological study. Three babies were referred for operative treatment which was successful in each instance. In two of these infants (Appendix: Baby 3, Series A and Baby 9, Series A) doubts were felt concerning the exact significance of the tumours. In one the tumour seemed to be minute in size although subject to violent and intensely hard spasmodic contractions. In the other the tumour was hard, of small as distinct from minute size, and unusual in being ring-shaped. At operation, small but appreciable tumours were found in each of these two cases. In the third baby (Appendix: Baby 18, Series A) the findings were wholly different. A large tumour was palpated which resembled in every respect, i.e., hardness, shape, rhythm, contraction and spasm, those felt in well established cases of true pyloric stenosis in older infants. Radiological screening showed acute gastric retention. At operation there was no visible tumour but complete symptomatic relief followed a Rammstedt operation.

This last case is evidence that a large, hard contractile tumour can be felt in the absence of organic change in the musculature of the pylorus. Despite the absence of organic change vomiting was unmistakably forcible and contributed to a loss of 1½ lb. in weight by the eighth day of life. By way of contrast tumours which eventually disappeared spontaneously, were felt in 16 symptomless infants. These cases would seem to provide further evidence that a palpable contractile pyloric tumour is not of itself proof of organic changes in the structure of the gastric musculature. Indeed, the finding of 25 tumours in a small control series of 115 healthy newborn infants suggests that the presence of a detectable tumour without associated symptoms is not uncommon.

If this view is accepted, the question arises, What is the significance of a tumour in such circumstances. If not evidence of organic muscular change is it evidence of disturbed gastric function? It is clearly impossible to draw any definite line of demarcation between normal and abnormal gastric motor function. The 25 infants in Series B in whom tumours were felt in the absence of symptoms cannot be said to have shown evidence of disturbed gastric function. This applies even to those few babies in whom peristalsis was seen and in whom the results of gastric lavage contained an unusual amount of mucus. On the other hand there are grounds for attaching greater significance to the tumours felt in infants included in Series A. In this series tumours were palpated in no fewer than 17 of the 21 babies and in each instance were associated with gastric symptoms, an unsatisfactory weight progress, pronounced peristalsis and excessive gastric secretion of mucus. Mucus in considerable amounts suggests gastric irritation. Visible pronounced peristalsis suggests intensified gastric motor activity and could be interpreted as a response either to local irritation or to an element of obstruction. If this explanation is correct, and if the suggestion (Cole Collaborators, 1932) that the circular muscular coat of the pyloric end of the stomach has a propulsive as well as a sphincteric function, frustrated peristaltic activity may well be followed by muscular spasm. Spasm of a segment of pyloric musculature would explain detection of a tumour, stimulated by filling of the stomach with a feed, into recurrent contraction and relaxation.

The presence of a detectable tumour cannot of itself be interpreted as evidence of disturbed gastric motor function. It is interesting, however, to note that among the infants who were screened, possibly abnormal motor function was a feature of 20 of the 25 infants with a palpable tumour and in only six of the 29 infants in whom no tumour was felt. Apparently disturbed gastric motor function was of two kinds: delay in the appearance of peristalsis and in emptying of the stomach, and notably vigorous peristaltic activity with extremely rapid passage of barium into the duodenum. In infants with a palpable tumour, vigorous motility was twice as common as delayed emptying of the stomach.

These observations might be accounted for by spasm of the pyloric musculature which could explain also the absence at operation of a contractile pyloric tumour previously palpated during clinical examination.

The radiological findings are interesting in view of Henderson's (1942) opinion that gastric motility is much more variable in the newborn than in adults; and of Smith's (1951) statement that the stomach empties more slowly in the newborn period than at any other time of life. Discussing the passage of fluid from the stomach Smith attaches less significance to gastric peristaltic activity than to what he describes as 'unpredictable relaxation of the pylorus and massive, gentle non-peristaltic movement'.

Opinions differ concerning the existence of pylorospasm as a separate clinical entity, and it is not mentioned in recent editions of a number of textbooks. Nelson (1954) suggests that pylorospasm is mistakenly applied to those infants in whom frequent and often violent vomiting is to be ascribed to abnormal excitability and overactivity. These were not features of infants studied in this investigation. Parmelee (1954), on the other hand, gives simple pylorospasm as a condition to be differentiated from pyloric stenosis, but discussing diagnosis states specifically that a tumour is not found in cases of pylorospasm. This opinion agrees with that originally advanced by Thomson (1921) who mentioned that in pylorospasm vomiting sometimes 'recurs at short intervals until the stomach is emptied'—a feature in several of the infants with tumours in the present study.

Wood and Astley (1952) in their study of vomiting of uncertain origin in infants, describe 12 babies in whom they attributed vomiting to pylorospasm. A tumour differing in consistence from that of the tumours of pyloric stenosis was felt in eight of their cases. Five infants were operated upon and found to have no hypertrophy. Wood and Astley do not discuss the possible nature of the tumour felt in these babies, but Astley (1952) is satisfied that infantile pylorospasm is a cause of occasional difficulty in radiological diagnosis. The cases described by Wood and Astley resemble those which are the subject of the present article in the association of a tumour with vomiting attributed to pylorospasm; but they differ in that the babies were older, fretful and in most instances artificially fed.

Remembering that this article is concerned with infants of less than 2 weeks of age, there is at least a possibility that one or more of the pyloric tumours operated upon were in fact evidence not of muscular hypertrophy but of muscular spasm. Mention has already been made of the two babies in Series A in whom very small tumours were found at operation (Appendix: Babies 3 and 9, Series A). Clinical diagnosis in each of these cases was one of pyloric stenosis. Immediate and dramatic clinical improvement followed Rammstedt operations. This of itself is not conclusive evidence that the very small tumours consisted of hypertrophied muscle tissue. No less dramatic and no less permanent improvement followed incision of the pyloric sphincter in the case in which no tumour was found at operation (Appendix: Baby 18, Series A). Instances have been reported (Browne, 1931; Thompson and Gaisford, 1935) of comparable results following Rammstedt operations on older infants in similar circumstances. On the other hand vomiting did not cease suddenly in an infant reported by Field (1941) and in two babies in Wood and Astley's series on whom Rammstedt operations were performed.

The purpose of this article is not to discuss the aetiology of pyloric stenosis but to stimulate investigation into the incidence and significance of palpable contractile pyloric tumours in the newly born. Although the present investigation consists of no more than a pilot study it is considered that contractile pyloric tumours can be palpated with unexpected frequency in the newly born, and that there is justification for believing that these tumours are usually evidence of muscular spasm and not muscular hypertrophy. The incidence of tumours in Series A and B was high. Were the clinical detection of a tumour evidence of organic muscular changes, it would be reasonable to expect pathological evidence of changes in the pyloric musculature in a proportion of newborn babies dying from whatever cause in the first two weeks of life. No such evidence was forthcoming as a result of Dr. Macgregor's detailed studies.

The significance to be attached to palpable contractile pyloric tumours in the newly born is of importance from the point of view of diagnosis, management and aetiology. That true pyloric stenosis can occur in the early days of life is unquestionable. A limited number of cases have been reported in newly born infants. Nevertheless, the incidence of tumours in the present study is far in excess of the believed incidence of pyloric stenosis in the newborn or, for that matter, in infants of any age. It might be argued that the tumours reported in this article were examples of hypertrophied pyloric musculature undergoing the spontaneous resolution which is known to occur in a proportion of older infants. In the light of experience with older infants, however, it is highly improbable that

any organic condition could be capable of such a high incidence of spontaneous resolution. Moreover, it is difficult to visualize resolution of an organic structural condition giving rise to the rapid clinical improvement characteristic of cases in Series A.

No reason can be advanced for the finding that a number of tumours in the present study were palpable for several weeks or months. Persistence was not accompanied by any symptoms. It is interesting to note in this connexion that Caffey (1945), discussing pyloric stenosis, states that radiological evidence of 'spasm of the antrum and stenosis of the pyloric channel may persist for years after surgical treatment and the complete relief of symptoms'.

Then, too, there is the possible significance of pylorospasm as a precursor or a contributory cause of pyloric hypertrophy. Findings in the present study do not suggest that a connexion exists between spasm and hypertrophy. Of infants with a tumour in the first two weeks of life none developed hypertrophic stenosis; and no tumour was palpated on examination on the eighth day of life in the only infant in the control series who later developed hypertrophic stenosis. Moreover, study of the notes of 23 infants operated on in general hospitals for pyloric stenosis revealed no connexion between progress during the first 12 days of life and the development of obstructive symptoms in later infancy.

Genetic Considerations. The significance of tumours encountered in the newborn is of importance also in relation to genetic studies. Present-day parents include many individuals who have recovered after operative treatment for hypertrophic pyloric stenosis in infancy. If, as has been suggested, heredity plays a part in the causation of pyloric stenosis (Carter and Savage, 1951) an increased incidence of the condition in infants can be expected (*Brit. med. J.*, 1954). It is important that future genetic studies do not attach too much significance to retrospective records of tumours in the early days of life which, although detected clinically and suspected radiologically, were not confirmed at operation.

Diagnosis. Finally, there is the vital question of decision as to treatment. A diagnosis of hypertrophic pyloric stenosis in the first two weeks of life calls for early operation. Contrary to what is experienced in older infants the utmost difficulty may be encountered in arriving at a final diagnosis despite repeated examination and despite radiodiagnostic help. The present study permits of no more than very tentative conclusions. These may be summarized as follows:

(1) Recurrent vomiting, failure to gain weight, visible peristalsis and a palpable tumour may be present in cases of pylorospasm or pyloric stenosis.

(2) Excessive gastric secretion of mucus is suggestive of pylorospasm rather than pyloric stenosis.

(3) Vomiting due to stenosis is usually more severe than that arising from pylorospasm, but this is not invariable.

(4) Vomiting due to stenosis, although copious, is unlikely to be truly projectile; it tends rather to be deliberate, resembling the flow from the spout of a tilted watering can.

(5) After a feed vomiting due to pylorospasm may occur once, twice or thrice at short intervals, whereas one copious vomit serves to empty a stomach obstructed by true stenosis.

(6) The tumour due to hypertrophic stenosis is harder and contracts more fiercely than that found in cases of pylorospasm; otherwise there is no constant distinguishing feature between tumours encountered in the two conditions.

(7) Recognizing that allowance must be made for exceptions, it can be said that in general the infant with pylorospasm fails to progress over a period of a few days while the condition of the baby with pyloric stenosis deteriorates progressively but not necessarily with great rapidity.

(8) Peristalsis tends to be more marked in cases of true pyloric stenosis.

(9) Observations concerning the stools have no reliable significance in differential diagnosis.

(10) Radiography has only a limited value in assessing the significance of a pyloric tumour in the first 10 to 14 days of life.

(11) Symptoms due to pylorospasm settle within a few days with treatment in the form of repeated gastric lavage. The need to try antispasmodic drugs did not arise in the present investigation, but should be kept in mind.

As already emphasized these conclusions are tentative. They are intended to apply only to infants of less than 2 weeks of age and are published in the hope that they will stimulate organized study.

Summary

A pilot clinical study intended to investigate the significance of palpable contractile pyloric tumours in newborn babies of under 2 weeks of age is described.

Clinical material consisted of two series of cases, 21 infants in whom failure to progress was associated with recurrent vomiting or regurgitation,

and 115 infants whose progress was satisfactory with no signs or symptoms of disturbed health.

Palpable contractile pyloric tumours were detected in 17 of the 21 infants in the first group and in 25 of the 115 infants in the second.

Details are given of the system of examination employed, the standards adhered to in determining the presence of a tumour, the methods of clinical management, and the results of *x*-ray screening.

The previously recorded neonatal histories of 23 infants who, after discharge from a maternity hospital, were subsequently operated on in general hospitals for pyloric stenosis are reviewed.

The results of follow-up studies are described.

The view is held that a palpable contractile pyloric tumour is present in a proportion of newborn infants in whom there is no organic disease.

It is suggested that in the absence of muscular hypertrophy the tumour is evidence of segmental spasm of the pyloric musculature, which is not to be regarded as necessarily evidence of abnormal function.

Instances of spontaneously subsiding recurrent vomiting (and regurgitation) in infants in whom tumours were felt are described and the suggestion made that these cases are examples of pylorospasm of a degree indicative of abnormal function.

Difficulties in the way of differentiating pylorospasm from hypertrophic pyloric stenosis in the early days of life are outlined, and tentative suggestions advanced.

No rigid conclusions have been arrived at and the purpose of the study is to focus attention on a subject which is considered to merit organized research.

APPENDIX

Summarized Clinical Observations on Certain Infants with Prominent Physical Characteristics and/or Severe Symptoms

Baby 3, Series A. Male, born in hospital, first child, birth weight 6 lb. 15 oz. Artificial feeding throughout; regurgitation on third and fourth day; frequent 'welling' but not projectile vomiting, with mucus, from seventh day; flat weight curve from second day. Spasmodic local thickening of pylorus palpated on tenth and eleventh day; minute 'tumour' with sudden phases of intense hardness felt on twelfth and thirteenth day; Rammstedt's operation performed on fourteenth day—very small tumour; subsequent progress uninterrupted (Fig. 1).

Baby 9, Series A. Male, born at home, second child, birth weight 7 lb. 12 oz. Breast fed throughout; frequent vomiting began on tenth day; admitted to hospital on 13th day. Frequent projectile vomiting, occasionally blood stained, copious mucus; fourteenth and fifteenth day pylorus felt but no tumour detected; sixteenth day pylorus notably firm; seventeenth day a very narrow, ring-like tumour felt to contract and relax as if in intense spasm; flat weight curve from admission; eighteenth day Rammstedt's operation—small tumour; subsequent progress uninterrupted.

Baby 11, Series A. Male, born in hospital, birth weight 7 lb. 9 oz. Breast fed. Regurgitation began on second day, and persisted until eighth day; occasional vomiting; excess mucus; tumour palpated on fourth, fifth and sixth days—spheroidal, hard and large—very easily felt and clearly defined. Weight curve flat from second to eighth day. Treatment limited to gastric lavage. Clinical improvement began in the second week of life. The tumour decreased gradually in size but was detectable until 10 weeks of age.

Baby 18, Series A. Male, born at home, first child, birth weight 7 lb.

Noticed to be exceptionally 'mucousy' from birth, excess mucus giving rise to retching and coughing. Offered breast and later expressed breast milk; all feeds exceeding 1 oz. in amount were immediately vomited. Stools infrequent and small. Admitted to hospital on eighth day of life markedly dehydrated and with weight of 5½ lb. Results of gastric lavage contained a very large amount of mucus and undigested curds; feeding followed rapidly by gross distension of stomach and later by forcible 'spouting' vomiting. Pronounced peristalsis; readily palpable, surprisingly large, firm contractile tumour of 'spinning top' shape. *X*-ray screening showed enormous gastric distension and delay in start of emptying for over 20 minutes. Laparotomy on ninth day of life; no visible tumour but Rammstedt's operation performed. Thereafter uninterrupted progress. Tumour not palpated on re-examination at the age of 1 month (Fig. 4).

Baby 14, Series B. Male, born in hospital, first child, birth weight 7 lb. 1 oz. Uneventful clinical progress from time of birth to last examination at the age of 4 months. Feeding at the breast throughout.

On sixth day of life tumour palpated—size of large pea, rhythmically contractile with filling of stomach, notably firm to point of hardness; no vomiting but considerable mucus in results of gastric lavage. Slight peristalsis. Examined at fortnightly intervals, tumour lessened in size and definition, disappearing at the age of 3 months.

Baby 97, Series B. Male, born in hospital, first child, birth weight 7 lb. 10 oz. Uneventful clinical progress apart from slight nasal catarrh in the second week. Breast feeding throughout.

On seventh day of life readily felt contractile tumour—small marble in size, spheroidal in shape, gradual contraction and relaxation, firm but not hard, minimal peristalsis. Examined at three weekly intervals, tumour disappeared gradually within six weeks.

I am indebted to the senior obstetrical staff of the Leeds Maternity Hospital for allowing me access to the babies of mothers under their care; to mothers of babies included in the control series for permission to examine

their babies; to Dr. A. R. Macgregor for pathological assistance and advice; and to Professor A. S. Johnstone and Dr. J. M. Winn for radiological help and reports. The enquiry would not have been possible without the enthusiastic help received from the nursing staff of Blackburn Ward, the Maternity Hospital, and I am especially grateful to the Departmental Sister, Miss M. Pattullo, and to Sisters M. J. Neasham and N. Sixsmith. Mrs. G. M. Turner (radiographer) gave great help in the making of arrangements for *x*-ray screening. I wish to acknowledge also help received in the course of discussion with Professor A. Durward and Dr. W. Goldie; and the reports of operative findings given me by Mr. H. S. Shucksmith. Dr. E. C. Allibone kindly lent records of infants admitted under his care in the General Infirmary: and Mr. L. Jolly, Librarian, The Royal College of Physicians, Edinburgh, gave me valuable assistance in providing references. I am greatly indebted to Miss J. Akester, Superintendent of Health Visitors, the City of Leeds Maternity and Child Welfare Department, and her colleagues for invaluable help in following up many of the babies.

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INFANTILE PYLORIC STENOSIS

BY

J. W. GERRARD, J. A. H. WATERHOUSE and D. G. MAURICE

From the Departments of Paediatrics and Child Health and Medical Statistics, University of Birmingham

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It would seem, from the studies of Carter and Powell (1954) and of McKeown, MacMahon and Record (1952), that both genetic and environmental factors play a part in the aetiology and development of infantile pyloric stenosis. The latter group of workers have stressed the importance of post-natal environmental influences. Their studies, based on data derived from more than 1,000 cases treated in the Children's Hospital, Birmingham, between 1940 and 1951, showed that symptoms, on average, developed later in babies born in hospital than in those delivered at home, and in first-born than in those born subsequently. In an earlier survey, based on 578 cases operated on between 1945 and 1950, they (McKeown *et al.*, 1951c) had also found that the size of the tumour was roughly proportional to the age of the baby at operation. These observations, coupled with the rarity with which the tumour is found at birth, strongly suggested not only that the growth of the tumour was a post-natal phenomenon, but also that its rate of growth was conditioned by post-natal factors.

The purpose of the present study was first to confirm, by direct measurement of the tumour at operation, that its size was indeed proportional to the age of the baby; secondly to enquire into possible post-natal influences determining its rate of development; and thirdly to attempt to evaluate the role of genetic factors.

Material and Methods

The pyloric tumour was measured at operation, using calipers and a metal ruler, in 51 cases selected at random during 1951 and 1952. The external dimensions (length and diameter of the tumour) were measured in all cases. The internal dimensions (the thickness of the muscle coat and the length of the incision) were measured in 43; the latter measurements were less easy to record accurately and variations in the thickness of the pyloric muscle were smaller, partly owing to retraction of the muscle after section and partly because the radius and not the diameter was being measured. These cases were analysed for factors influencing tumour size. A further 101 cases, treated between 1949 and 1953, were taken at random from the hospital files and together with the first series were subjected to careful examination for possible post-natal environment factors affecting the rate of development of symptoms.

Results

Size of Tumour at Operation.—The data are represented diagrammatically in Fig. 1. The size of the pyloric tumour (external measurements) was found to be closely correlated with the age of the infant at operation, confirming McKeown's observations. Tumour size was also correlated with duration of symptoms, but not with weight. Thus,

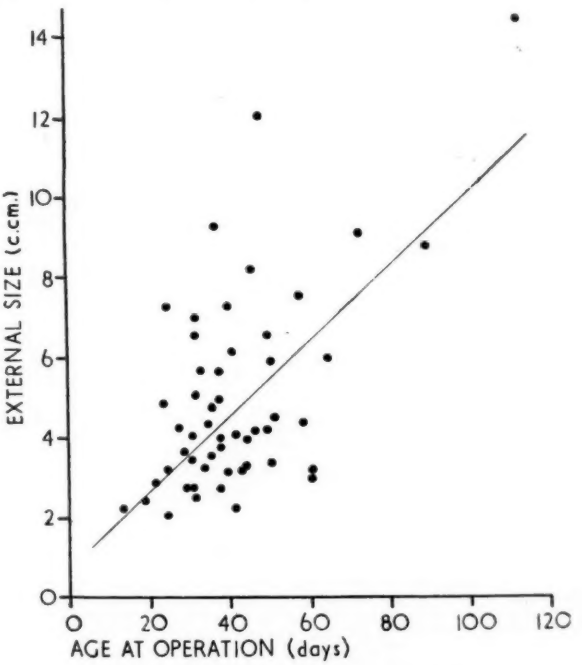

FIG. 1.—Scatter diagram and regression line relating external size of tumour to age at operation.

duration of symptoms, tumour size and age at operation were all correlated. Within certain assumptions the method of partial correlation can be used to remove the effects of a common factor and to discover the remaining relationship between two variables. When this was applied it was found that the correlation between external dimensions and age at operation remained significant when the effect of duration of symptoms was removed, but not *vice versa*. There was no close correlation between the internal dimensions of the tumour and the age at operation, probably because the measurements themselves were less accurate, for reasons already stated, and because differences between large and small tumours were less conspicuous on internal size.

Environmental Factors: Frequency of Feeds. When analysing the 51 cases whose tumours were measured at operation, it was noted that the four premature infants in this group developed their symptoms—usually vomiting—almost as quickly as the full-term babies in the series. The four premature babies were born, on average, five weeks before the expected date of delivery, but they developed their symptoms only five to 10 days later than their full-term counterparts. It was concluded, therefore, that the environmental factor influencing the rate of development of symptoms was brought into play at a comparatively early age even in the premature babies; it was suspected that this factor might be related to feeds. The introduction of food into the stomach, especially if rich in fat, like milk, is known to stimulate pyloric contraction. It seemed quite possible that more frequent feeding schedules might be associated with the earlier onset of symptoms, and less frequent feeding schedules with a later onset of symptoms.

All cases under analysis were, therefore, divided into two groups, those fed three-hourly and those fed four-hourly (Table 1). It is seen that the babies fed three-hourly developed their symptoms significantly earlier than those fed four-hourly. The mean age when vomiting first started in those fed three-hourly was 21·6 days (after approximately 129 feeds) and 27·1 days (after approximately 135 feeds) in those fed four-hourly. The mean birth weight, as might be expected, was rather less in those fed three-hourly (average 7·1 lb.) than in those fed four-hourly (average 7·7 lb.); nevertheless, the correlation between birth weight and the age when symptoms first developed was negligible. It should be noted that the mean age when vomiting first started was not, apparently, influenced by the place of birth. Those fed three-hourly, whether born at home or in hospital, started to vomit on average on the 22nd day, and those fed four-hourly started to vomit on the 27th or 28th day. The differences between the rate of development of symptoms in those born at home and in hospital and fed three-hourly (0·2 day) and fed four-hourly (0·7 day) are insignificant, though in both instances it is the baby born in hospital who begins to vomit later.

A comparison of the feeding schedules of babies born at home and in hospital reveals (Table 1) that of those born in hospital (in Birmingham) approximately only one-third are fed three-hourly, whereas of those born at home nearly one half are fed three-hourly during the first few critical weeks. This, no doubt, explains the earlier onset of symptoms in those born at home. Further analysis has shown that birth rank also influences the rate of development of symptoms (Table 2), second and third births tending on average to develop their symptoms increasingly early. The acceleration of the onset of symptoms, which is not apparent in fourth and subsequent births, is greatest in those fed three-hourly, and is not influenced by the place of birth.

TABLE 1

AGE AT ONSET OF VOMITING IN RELATION TO FEEDING SCHEDULE AND PLACE OF BIRTH

Feeding Schedule	Place of Birth		Hospital and Home
	Hospital	Home	
3-hourly	21·7 days (30)*	21·5 days (25)	21·6 days (55)
4-hourly	27·3 days (66)	26·6 days (31)	27·1 days (97)
3- and 4-hourly ..	25·6 days (96)	24·3 days (56)	

* Figures in parentheses refer to numbers of cases.

TABLE 2

MEAN AGE AT VOMITING IN DAYS

Birth Rank	3-Hourly	4-Hourly	Total
1	24·5 (17)*	30·8 (37)	28·9 (54)
2	21·1 (17)	24·9 (30)	23·5 (47)
3	17·9 (10)	24·2 (18)	22·0 (28)
4+	21·1 (11)	25·4 (12)	23·4 (23)

* Figures in parentheses refer to numbers of cases.

Genetic Factors. There are two factors which are difficult to reconcile with the suggestion that pyloric stenosis is genetically determined; first that there appears to be an excess of first-borns (McKeown *et al.*, 1951a), and secondly that there is no greater incidence of the disease in first cousins than in the general population (McKeown *et al.*, 1951b). With

regard to the second observation we have no additional data to offer; with regard to the first we have. We compared the distribution of our cases by place of birth—home or hospital—with that for Birmingham as a whole during the same period, viz., 1949-1953 (Padley, 1954). The agreement was found to be close, and the sample, therefore, a fair and unbiased one. We found, however, no increase of first births over expectation (Table 3). In fact the distribution by birth rank is remarkably close to expectation, particularly in males.

TABLE 3
INCIDENCE OF PYLORIC STENOSIS BY BIRTH RANK COMPARED WITH THE EXPECTED INCIDENCE*

Birth Rank	Both Sexes		Males	
	Observed	Expected	Observed	Expected
1	54	57·9	50	48·8
2	47	43·8	37	36·9
3	28	23·7	22	20·0
4	13	11·9	12	10·0
5	4	6·2	2	5·2
6+	6	8·6	5	7·1
Total ..	152	152·1	128	128·0

* From City of Birmingham *Annual Abstract of Statistics*, Vol. 2.

Discussion

We have been able to confirm the findings of McKeown *et al.* (1951c) that the size of the pyloric tumour is proportional to the age of the baby at the time of operation.

We have also shown that the earlier onset of symptoms in babies born at home, and its later onset in those born in hospital, and also in first births, would seem to be due simply to difference in feeding schedules. Most babies delivered in hospital—and this includes a high proportion of first births—are fed four-hourly; such babies tend to develop symptoms late. A higher proportion of babies born at home are fed three-hourly, and such babies tend to develop symptoms early. It would seem that the more frequently a baby is fed, other things being equal, the sooner will symptoms develop. The baby's early environment, whether in the home or in hospital, apart from its influence on the frequency with which feeds are offered, appears to have no demonstrable effect on the rate at which symptoms develop. Since feeding is the necessary stimulus for the development of the tumour it is not surprising that it has been observed only exceptionally at birth or soon after, for babies probably do not imbibe much fluid *in utero*.

Whether the quality of the feed offered, human or cow's, half-cream or full-cream milk, is also of aetiological import we are unable, as yet, to say. The feeding régimes of the babies in our series were very variable; many began life on human milk and later were offered, either because the maternal supply was subsiding, or because the baby was beginning to vomit, feeds derived ultimately from the cow. As has already been mentioned, premature babies, although fed three-hourly, do not always develop their symptoms as rapidly as might be expected. This may be because there is often a delay of two or three days before feeds are first introduced in prematures, but it may also be because premature babies are usually given dilute feeds, which are low in fat. It is unlikely to be due to the fact that these babies are kept in hospital longer than full-term babies, for, as we have shown, the place of birth in itself is unimportant.

Variations with which feeds are offered may explain the discrepancies to which McKeown has drawn attention between babies born at home and those delivered in hospital, but they cannot explain why a tumour develops in the first place, for all babies are fed, and only three per 1,000 develop a tumour.

The findings of MacMahon and McKeown (1955) in their study of pyloric stenosis in twins, that there is no increased incidence in monozygous twins, makes it very difficult to postulate that genetic factors have any direct bearing on the aetiology of this disorder. A further study by these authors (McKeown and MacMahon, 1955) on the incidence of pyloric stenosis in parent and child draws attention to the interesting fact that it is as common in the mother as it is in the father of an affected child. In the parents the ratio of male to female is 1 : 1; in the children it is, as expected, 4 : 1. The same relationship is present in the group of cases studied by Carter and Powell (1954), but they did not comment on it. The unexpectedly high frequency of the disorder in the mother suggests that she has a greater influence in the production of the disease in her child than the father. This influence may be in part perinatal, or milk-borne, or perhaps even psychological. Though psychological factors may be pertinent, they are difficult to evaluate and should take second place, in our view, to a more detailed investigation of feeding and ingredients of the milk. A clue to the aetiology of the disorder may be given by the knowledge that whatever stimulates pyloric hypertrophy and contraction is inhibited by atropine methyl nitrate.

Summary

The size of the pyloric tumour is proportional to the age of the baby at operation.

The rapidity with which symptoms develop is related to the frequency with which the baby is fed;

babies fed three-hourly develop symptoms on average in 21·6 days, babies fed four-hourly develop symptoms on average in 27·1 days.

We have not found any increased incidence of the disease in first-borns.

We are grateful to Dr. Padley of the Central Statistical Office of the City of Birmingham, for generously giving us access to his material, to the staff of the Children's Hospital, Birmingham, for allowing us to study their patients, and to Professor McKeown and Dr. MacMahon for reading a draft of this paper and for allowing us to see the typescripts of two of their papers.

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INFANTILE HYPERTROPHIC PYLORIC STENOSIS IN PARENT AND CHILD

BY

THOMAS McKEOWN and BRIAN MacMAHON
From the Department of Social Medicine, University of Birmingham

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In a recent report, Carter and Powell (1954) recorded 12 examples of pyloric stenosis in parent and child, and drew attention to the increased risk of the disease in offspring of parents who were themselves affected. In examining their observations we noted that the risk to the child seemed to be greater if the affected parent was the mother; but the number of cases was small, and the matter evidently required investigation in a larger series. Nielsen (1954) has since recorded nine examples of pyloric stenosis in parent and child, to which we have been able to add a further 12. The results support the conclusion that the risk is raised in children of affected parents, and suggest that it is much higher if the affected parent is the mother.

Incidence in Offspring of an Affected Parent

There were 491 patients in whom the diagnosis of pyloric stenosis was confirmed by operation at the Birmingham Children's Hospital in the period 1920-34. One hundred and twenty-eight (26·1%) died in hospital, and a further 33 lived more than 15 miles from the city. Of the remaining 330 patients, 129 were traced; 17 of them had died since discharge from hospital. Unfortunately, most of the 112 patients interviewed were treated in the later years of the period, so that the number of offspring born before the time of enquiry was small, 29 in 23 families. None of them had had pyloric stenosis.

Carter and Powell (1954) found three cases of pyloric stenosis among 46 children of 28 patients treated at The Hospital for Sick Children, Great Ormond Street, between 1920 and 1929, and Nielsen (1954) found 11 cases among 128 children of 95 patients. In the three series there are 14 affected among 203 children, an incidence of 6·9%.

Sex of Affected Parents

Although no examples of pyloric stenosis in parent and child were found by tracing Birmingham patients treated between 1920 and 1934, eight were ascertained by inspection of recent records of children with the disease. Four of these families were previously recorded among cases treated in the period 1940-49 (McKeown, MacMahon and Record, 1951): in two (both mothers) the parent was operated on; in the other two cases (one mother and one father) the diagnosis rested on medical evidence only. Four more families were found in records of the Birmingham Children's Hospital for the years 1950-54, three in which the mother had been submitted to operation, and a fourth in which the condition was diagnosed medically in a father. Two other Birmingham families (operation on mother and child), identified by postal enquiry, are referred to below.

In an attempt to increase the number of cases, records of 2,579 recent patients were inspected in hospitals in Liverpool, Manchester, Newcastle-on-Tyne and Sheffield (see acknowledgments). Only two more examples were ascertained; in both cases the father was affected and the diagnosis was confirmed at operation.

Details of the 12 families are given in Table 1; in eight the parent affected was the mother. In

TABLE 1

12 FAMILIES WITH PYLORIC STENOSIS IN PARENT AND CHILD

Number	Parent Affected	Sex of Children
1	Mother†	M*
2	Mother*	M* M
3	Mother*	M† F*
4	Mother*	M*
5	Mother*	F M*
6	Mother*	M*
7	Mother*	M M*
8	Mother*	M*
9	Father†	a a F* M*
10	Father†	M*
11	Father*	M* M*
12	Father*	F*

* = operated, † = treated medically for pyloric stenosis, a = abortion
(Families 1, 2, 3 and 9 are Nos. 49, 337, X10 and 223, respectively, in the appendix published by McKeown *et al.*, 1951.)

TABLE 2

SEX OF AFFECTED PARENT IN FAMILIES WITH PYLORIC STENOSIS IN PARENT AND CHILD

Source	Parent Affected*		Parent Affected†		Total	
	Mother	Father	Mother	Father	Mother	Father
Birmingham data ..	7	2	1	2	8	4
Carter and Powell (1954) ..	5	6	1	0	6	6
Nielsen (1954) ..	0	0	3	6	3	6
Total ..	12	8	5	8	17	16

* = operated, † = treated medically for pyloric stenosis

Table 2 the results are combined with those of the two previous series. In 17 of 33 families in which pyloric stenosis was diagnosed in the parent of a patient, it was the mother who was affected. The diagnosis was confirmed at operation in 20 parents, of whom 12 were mothers and eight fathers.

It will be recalled that the proportion of males among children with pyloric stenosis (about 80%) has been remarkably constant in all published series, and it would therefore be expected that the number of fathers affected would be approximately four times as great as the number of mothers. The difference between the observed (52%) and expected (20%) proportions of mothers in this rather small series is highly significant ($32 \pm 7\%$).

Before discussing the interpretation of this observation we must consider the possibility that it arises from a defect in the method of collecting the data. Most of the familial cases were derived from hospital records, provided as a rule by the mother, whose knowledge of her husband's childhood illnesses may be less complete than her knowledge of her own. In an attempt to discover whether the number of affected fathers was deficient, questionnaires were sent by post to fathers of 394 patients treated for pyloric stenosis at the Birmingham Children's Hospital in the years 1950-54. Notes of these patients had previously indicated that three mothers were certainly, and one father possibly, affected. Replies were received from 321 fathers (54 other questionnaires were returned uncompleted because of a change of address). No further examples of affected fathers were ascertained. Five fathers stated that their wives had been affected. Three of these cases had previously been identified from hospital notes; both the new cases were said to have been operated on for pyloric stenosis, although it was possible to inspect operation notes in only one of them. It is concluded that there is no reason to suppose that the number of affected fathers is deficient.

Several possible explanations can be suggested for the observation that the proportion of mothers among affected parents is much higher than the expected 20%. (*a*) The proportion of males among patients with pyloric stenosis may have been lower in the period 1920-30 than it is today. (*b*) Survival rates may have been higher for female than for male patients. (*c*) Fertility may be greater in affected females than in affected males.

The first two possibilities can be dismissed by examination of the sex ratio of the patients treated at the earlier period and traced. In our own series there were 89 males and 23 females; Carter and Powell (1954) traced 73 and 12, and Nielsen (1954) 73 and 22, males and females respectively. The proportion of males is approximately as would be expected if the sex ratio were the same at the earlier period and if there were no appreciable sex difference in survival rates.

There is also no reason to believe that fertility was lower in men than in women. In our own series the 89 patients had 26 children, and the 23 females had three. Carter and Powell recorded 39 children of 73 affected fathers, and seven of 12 affected mothers. (This information was not given by Nielsen.) In the two series combined, 162 males had 65 children (0·40 per father) and 35 females had 10 (0·29 per mother). On this evidence fertility is somewhat lower in women than in men, and, since mean age at marriage is probably also lower, it is possible that the difference in fertility between the sexes is a little greater than the data suggest.

It is concluded that the risk of pyloric stenosis is considerably greater (at least four times) in children of affected mothers than in children of affected fathers.

Incidence in Offspring when Parent and Child are Affected

The incidence of pyloric stenosis in children of affected parents was given above as 6·9% (14 in 203). In families where one child is affected the incidence in other children is evidently much greater than this. Eight of the 33 second-generation fraternities shown in Table 2 contained more than one affected member.

All 33 fraternities are identified by the presence of at least one affected child. In these circumstances the numbers of affected children to be expected in the fraternities on the assumption that the risk is the same as that experienced by all children of affected parents (6·9%) has been estimated (Table 3) by a method described by Hogben (1931). The number of affected children observed (42) is higher than the expected number (34·3). By the same method it is possible to show

TABLE 3

OBSERVED AND EXPECTED NUMBERS OF CHILDREN WITH PYLORIC STENOSIS IN FAMILIES WITH A PARENT AND CHILD AFFECTED

Size of Family	No. of Families	No. of Children	Number of Children Affected	
			Observed	Expected*
1	11	11	11	11·00
2	14	28	19	14·50
3	4	12	5	4·29
4	3	12	4	3·33
6	1	6	3	1·19
Total ..	33	69	42	34·31

* Expected proportions affected for each family size are: $\frac{r}{1-(1-r)^s}$, where r is the risk to children, and s is family size (Hogben, 1931).

that in these fraternities, distinguished by the presence of pyloric stenosis in parent and child, the proportion of the children who may be expected to have the disease is 39%. Clearly the risk is not spread uniformly among all offspring of parents who have had pyloric stenosis, but is highly localized in certain families.

Discussion

Until recently it was thought that infantile hypertrophic pyloric stenosis was attributable to a recessive gene whose manifestation is influenced by sex and birth order (Cockayne and Penrose, 1943). McKeown, MacMahon and Record found no evidence to support the recessive hypothesis (1951) and showed that the post-natal environment affects both time of onset of symptoms and the increased risk experienced by first-born children (1952). Nevertheless, it is still widely believed that pyloric stenosis is an inherited condition whose aetiology can profitably be discussed in terms of a simple genetic hypothesis. Evidence from three sources has been thought to support this conclusion: investigations of familial incidence; comparison of the frequency of concordance in monozygous and dizygous twins; and examination of relative incidence in male and female children.

That the incidence of pyloric stenosis is raised in certain families is shown by the increased risk experienced by (*a*) brothers and sisters of an affected child (Cockayne and Penrose, 1943; McKeown *et al.*, 1951), and (*b*) children of affected parents (Carter and Powell, 1954; Nielsen, 1954). But it by no means follows that the familial tendency is genetically determined. Many features of the post-natal environment must be common to consecutive children of the same mother, and whether the increased risk in later sibs of an affected child is attributable mainly to a common inheritance or to a common environment is at present an open question. Nor is it difficult to conceive that the early post-natal environment of a child is in some cases identified with that of its parents; the occasional presence of a grandmother is sufficient to ensure this. But perhaps the strongest reason for doubting whether the increased incidence of pyloric stenosis in children of affected parents is determined by inheritance is that the risk is greatly increased if the affected parent is the mother. It is also clear that the risks are by no means equal in all families in which a parent has had the disease, but are highly localized in certain families. These observations cannot be reconciled with any simple genetic hypothesis; they are readily explained if the varying risks of the disease are determined by the environment.

It has also been thought that when pyloric stenosis occurs in one twin, the other twin is almost invariably affected if the pair is monozygous and rarely affected if it is dizygous (Sheldon, 1938). A number of exceptions to this generalization have now been reported, and indeed examination of a representative series suggested that the frequency of concordance is probably about the same in monozygous and dizygous twins (MacMahon and McKeown, 1955). The previous result is apparently attributable to the unrepresentative character of twin pairs reported in the literature.

As evidence of the influence of inheritance on the origin of pyloric stenosis, we are left with the undoubted higher incidence in male than in female children. But several features of the condition are incompatible with sex-linked inheritance, and the sex difference in incidence must presumably be attributed to genetic processes whose nature cannot be specified. In this respect pyloric stenosis is characteristic of a class of diseases, of which peptic ulcer is an example, in which susceptibility is different in the two sexes, but is certainly not due to a single gene.

Summary

One hundred and twelve living patients in whom the diagnosis of pyloric stenosis was confirmed by operation at the Birmingham Children's Hospital in the period 1920-34 were traced in 1955. They had 29 children, none of whom had pyloric stenosis. By combining these results with those from two reported series, the incidence of the disease in children of affected parents is estimated as 6·9%.

Ten cases of pyloric stenosis in parent and child were obtained from current records of children treated at the Birmingham Children's Hospital. By inspection of notes of 2,579 patients treated in

hospitals in Liverpool, Manchester, Newcastle-on-Tyne and Sheffield a further two examples of the disease in parent and child were ascertained. In eight of the 12 families the affected parent was the mother. When the results are combined with those of two published series there are 33 families; in 17 the mother was affected. Since pyloric stenosis is much more common in males than in females it is concluded that the risk of the disease is considerably greater (at least four times) in children of affected mothers than in children of affected fathers.

It is also shown that the risk of pyloric stenosis is not spread uniformly among all offspring of parents who have had the disease, but is highly localized in certain families. Among children in families in which a parent and one child have been affected, the proportion exhibiting the disease is approximately 40%.

It is suggested that these results are inconsistent with a simple genetic hypothesis, and are more plausibly attributed to the influence of the early post-natal environment.

We are indebted to the administrative and medical staffs of the hospitals who gave permission to examine records, and to Professor N. B. Capon (Liverpool), Dr. A. Holzel (Manchester), Professor R. S. Illingworth and Dr. T. Colver (Sheffield) and Dr. George Davison (Newcastle) for making the necessary arrangements. We are particularly indebted to Dr. George Davison for allowing us to review his records of 1,100 patients in Newcastle over a long period.

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KERNICTERUS AND PREMATURITY

BY

V. M. CROSSE, T. C. MEYER and J. W. GERRARD

From Sorrento Maternity Hospital, Birmingham

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At one time kernicterus was most commonly associated with haemolytic disease of the newborn. With the introduction of adequate exchange transfusions this complication, whether due to Rh or to ABO incompatibility, has been virtually eliminated. In 1950 two groups of workers, Aidin, Corner and Tovey in this country and Zuelzer and Mudgett in America, independently drew attention to the fact that kernicterus was sometimes associated with prematurity only. Other workers (Gerrard, 1952; Govan and Scott, 1953) have also given details of cases and suggested possible aetiological factors.

The present paper draws attention to the early signs of the disease, its mortality and the sequelae in survivors. An attempt has also been made to assess its incidence, its relationship to such factors as sex, birth weight, maturity and birth order, and ante-natal and post-natal factors. Among the post-natal factors specifically studied has been the level of the serum bilirubin in those developing kernicterus; these levels have been compared with those in normals.

Material and Methods

Three groups of babies have been studied. First, 60 premature babies in three Birmingham units who developed kernicterus in the absence of iso-immunization during the years 1951-54. Kernicterus was demonstrated either at necropsy in those who died in the neonatal period or by follow-up studies in the survivors. These cases have been compared first with 60 controls (a control was the first baby in the same 500 g. weight group admitted to the same premature baby unit after the case developing kernicterus), secondly, when possible, with all the premature babies (2,608) admitted to the units during the same period.

A second group of 91 children has been studied to assess the importance, if any, of blood group incompatibility between the mother and child. This group was composed of 56 dying in the neonatal period, in which the diagnosis was confirmed at necropsy, and of 35 who survived with varying degrees of choreoathetosis and perceptive deafness. The latter had all been deeply jaundiced in infancy, and their history was characteristic of kernicterus as seen in prematures. This group included the 60 cases already mentioned. Iso-immunization was excluded by a negative direct Coombs test on the baby's blood in 59 instances; by the absence of any anomalous agglutinins and of immune anti-A and anti-B in the maternal serum in 83; and by a negative indirect Coombs test, using maternal serum and either the infant's or the father's red cells, in 50.

A third group of cases has been studied to determine whether there is any relationship between the degree of jaundice and the development of kernicterus. This group included 46 normal full-term and 47 premature babies. The serum bilirubin was estimated on the second, fourth and sixth days. The mean serum bilirubin levels in babies of different birth weight groups were then calculated. Twelve premature babies who developed kernicterus in the absence of iso-immunization were also studied; these 12 were all included in the first group of 60. The total, direct and indirect, serum bilirubin levels were estimated on venous blood by the method of Malloy and Evelyn (1937).

Results

The following results are based on our findings in the first group of prematures.

The Signs of Kernicterus. The first 24 or 48 hours of life in the premature baby are the most critical, but once these are passed the chances of ultimate survival are good. The signs of kernicterus (Table 1) develop in a baby who is jaundiced after this initial adjustment to an extra-uterine environment. The signs include head retraction, an expressionless facies, usually with oculogyric movements, changes in muscle tone, cyanotic attacks, a refusal to suck in those bottle-fed, vomiting and, terminally, haemorrhage, usually from the mouth.

In severe cases these signs are self evident, but in those less affected they are easily missed. Jaundice may be overlooked, especially in artificial light, because the plethoric colour of prematures tends to conceal the underlying icterus. If the skin, however, is stretched between two fingers, jaundice becomes immediately apparent. Oculogyric move-

TABLE 1
SIGNS OF KERNICTERUS

	Number of Babies Showing Sign	
	Kernicterus (60)	Controls (60)
Jaundice (marked degree) ..	38	2
Head retraction ..	38	—
Expressionless face ..	approx. 40	—
Oculogyric crises ..	approx. 40	—
Muscle tone changes	31	—
(*a*) Hypertonic ..	19	—
(*b*) Hypotonic ..	12	—
Cyanotic attacks ..	34	12
Anorexia	30	5
(Bottle-fed babies who had to be tube-fed)	of 46 bottle fed	of 38 bottle fed
Vomiting	31	2
Terminal haemorrhage	8	—
(*a*) from mouth ..	7	—
(*b*) melaena ..	1	—

ments of the eyes are also characteristic, but they may not be noticed unless specifically sought; the eyes tend to roll down and give a 'setting sun' appearance. A baby who exhibits any of the signs enumerated above, especially between the fourth and eighth days of life, is re-examined at regular intervals by us for at least one year, even if he appears normal on discharge. Several babies who showed minimal signs have proved to be definite cases of kernicterus.

The Time of Onset of Kernicterus. All but four of the 60 cases developed kernicterus between the fourth and eighth days of life; in nearly half the onset was on the sixth day (Table 2). In the 1,000-1,500 g. weight group more cases occurred before the sixth day than after; in the 1,500-2,000 g. weight group equal numbers occurred before and after this day; in the heaviest weight group, 2,000-2,500 g., more cases occurred after the sixth day than before. The onset tended to be later as the birth weight increased.

Neonatal Mortality and Kernicterus. During the period under study, 17% of the controls and 25·6% of all premature babies admitted, died, but of the 60 cases of kernicterus, 73% (44) died. With the exception of the 2,000-2,500 g. group, the mortality from kernicterus decreased as birth weight increased (Table 3). The high mortality in the 2,000-2,500 g. group is probably due to the fact that babies over 2,000 g. are only admitted if in poor condition.

TABLE 3
NEONATAL MORTALITY AND KERNICTERUS

Weight (g.)	Kernicterus		All Prematures Admitted	
	Neonatal Death		Neonatal Death	
	Total	No.	Total	No.
Up to 1,000 ..	3	3 (100%)	120	104 (87%)
1,000 to 1,500 ..	18	16 (89%)	405	206 (51%)
1,500 to 2,000 ..	24	13 (54%)	1,123	236 (21%)
2,000 to 2,500 ..	15	12 (81%)*	960	122 (12·7%)*
Total	60	44 (73%)	2,608	668 (25·6%)

* Babies weighing over 2,000 g. are only admitted if ill and this accounts for the high mortality in this weight group.

Generally speaking, the earlier the onset, the higher the mortality, but this may be accounted for by the earlier onset among the smallest babies (Table 2).

Sequelae in Survivors. Sixteen of the 60 cases of kernicterus survived the neonatal period. The majority were hypotonic in the neonatal period, while a few remained hypertonic and lay with the head thrown back. A few weeks later all appeared to be normal.

Follow-up examinations were carried out at the 'corrected ages' of 6, 12 and 18 months, the 'corrected age' being the chronological age plus the number of weeks that the child was born before the expected date of delivery.

AT 6 MONTHS. All babies were re-examined at this age. The majority were irritable, did not sleep well and cried a great deal. Twelve had spells of opisthotonos, 10 exhibited some degree of

TABLE 2
DAY OF ONSET OF KERNICTERUS

Day of Life	Birth Weight Groups				
	Up to 1,000 g.	1,000-1,500 g.	1,500-2,000 g.	2,000-2,500 g.	Total
3	—	—	1 (died)	—	1 (died)
4	1 (died)	6 (6 died)	3 (2 died)	1 (died)	11 (91% died)
5	—	—	4 (3 died)	—	4 (75% died)
6	1 (died)	8 (6 died)	8 (3 died)	11 (9 died)	28 (68% died)
7	—	3 (3 died)	3 (2 died)	1 (died)	7 (86% died)
8	1 (died)	—	3 (1 died)	2 (1 died)	6 (50% died)
9	—	—	2 (1 died)	—	2 (50% died)
After 9	—	1 (died)	—	—	1 (died)
Total	3 (3 died)	18 (89% died)	24 (54% died)	15 (81% died)	60 (73% died)

eye-rolling. All had been late in smiling, holding their heads up and taking solids. When lowered into the prone position, 13 still went into the knee-chest position, and when in the prone position, with the hips extended and knees flexed, the babies still responded to stroking of the soles by hip flexion, i.e., by the withdrawal reflex. Muscle tone was variable.

AT 12 MONTHS. The three most severely affected babies died with severe rigidity and hyperpyrexia before reaching this age, and three have left the area. Of the remaining 10 babies, eight were less irritable and were sleeping better. Feeding difficulties were still present in five, opisthotonos in six and oculogyric movements in four. All were backward in reaching the recognized milestones: only two were able to sit without support, and only one could stand alone. Hearing was probably impaired in seven. Speech was delayed in all, and so was mental development.

AT 18 MONTHS. Six babies have now reached this age. These six appear contented. Five are definitely hypotonic, and in two of these athetoid movements are beginning to develop. Three still exhibit spells of opisthotonos and oculogyric movements. The withdrawal reflex is still present in four. Two can sit without support; one of these has good head control and can stand by himself. Speech is delayed in all, one can say recognizable words, and this is the only child whose hearing appears to be unimpaired. Mental development is delayed in all.

Dental Development. None of the children have green teeth. In only one are the canines fully erupted. In this the junction between the hypoplastic pre-natal and well calcified post-natal enamel can be clearly seen on the canines half way between the incisal edge and the gingival margin.

TABLE 4

KERNICTERUS AND BIRTH WEIGHT

Birth Weight (g.)	All Prematures Admitted		Kernicterus		
	Total	Babies at Risk (48-hour Survivors)	Total	Percentage of Total	Percentage of Babies at Risk
Up to 1,000 ..	120	43	3	2·5	7·0
1,000 to 1,500 ..	405	266	18	4·4	6·8
1,500 to 2,000 ..	1,123	972	24	2·1	2·5
2,000 to 2,500 ..	960	900	15	1·6	1·7
Total ..	2,608	2,181	60	2·3	2·8

Factors with a Bearing on Aetiology. Table 4 shows (*a*) all prematures admitted during the four-year period 1951-54, and (*b*) the 60 cases of kernicterus, divided into 500 g. birth weight groups. With the exception of those weighing less than 1,000 g. at birth, the incidence of kernicterus decreased as the birth weight increased. Because many premature babies, especially those weighing less than 1,000 g. at birth, die before they can develop kernicterus, the incidence of this complication is also determined among those surviving the first 48 hours; the incidence was highest in those weighing less than 1,000 g. at birth. The incidence of kernicterus was, therefore, inversely proportional to the weight at birth among the babies at risk.

MATURITY. The relationship of kernicterus to maturity is shown in Table 5. The incidence of kernicterus was inversely proportional to maturity both for all prematures and for those surviving the first two days.

TABLE 5

KERNICTERUS AND MATURITY

Maturity in Weeks	All Prematures Admitted		Kernicterus		
	Total	Babies at Risk (48-hour Survivors)	Cases	Percentage of Total	Percentage of Babies at Risk
Up to 30 ..	264	109	11	4·2	10·1
31 to 32	386	282	16	4·2	5·7
33 to 34	801	685	22	2·7	3·2
35 to 36	792	749	8	1·0	1·1
Over 36	365	356	3	0·8	0·8
Total ..	2,608	2,181	60	2·3	2·8

BIRTH ORDER. When the cases of kernicterus are compared with the 60 controls and with all the premature babies admitted during the same four-year period (Table 6), it is seen that there is no appreciable difference between the three series in regard to the percentage found in each birth rank.

TABLE 6

KERNICTERUS AND BIRTH ORDER

Birth Order	Kernicterus		Controls		All Prematures Admitted	
	Total	Percentage	Total	Percentage	Total	Percentage
1	20	33·3	19	31·7	879	33·7
2	13	21·7	15	25·0	725	27·8
3	10	16·7	9	15·0	436	16·7
4	8	13·3	8	13·3	175	6·7
5	3	5·0	5	8·3	125	4·8
6+	6	10·0	4	6·7	268	10·3
Total ..	60	100·0	60	100·0	2,608	100·0

It can be concluded, therefore, that birth rank does not have any influence on the development of kernicterus.

SEX. An excess of females is usual among prematures because, on average, females weigh less than males at each stage of gestation. As expected, therefore, there was a slight excess of females among the 60 controls; 55% were female. This was in very close agreement with the distribution among all prematures born in the City of Birmingham during the same four-year period, of whom 54·7% were female. Among the cases of kernicterus, however, there was a preponderance of males; only 42% were female.

MULTIPLE BIRTH. Table 7 shows that there was no significant excess of multiple births among the

TABLE 7
KERNICTERUS AND MULTIPLE BIRTH

	Kernicterus	Controls	All Prematures Admitted
1st born twin ..	4 babies	7 babies	273 babies
2nd born twin ..	11 babies	6 babies	277 babies
Triplet	—	—	27 babies
All multiple born	15 = 25·0%	13 = 21·7%	577 = 22·1%

affected babies. When a twin developed kernicterus, the second was more frequently affected than the first. This was not due to any marked difference in the weight of the baby, for the average birth weight of those affected was 1,600 g., and of those unaffected was 1,650 g. The sex distribution among affected cases was approximately equal, eight were male and seven female; four pairs were MM, three FF and seven MF. Only once did both twins develop kernicterus; one was male, the other was female.

COMPLICATIONS OF PREGNANCY. Table 8 shows the main complications of pregnancy for the cases of kernicterus, the controls and all admissions.

TABLE 8
COMPLICATIONS OF PREGNANCY

Complication	Kernicterus (60)	Controls (60)	All Prematures Admitted (2,608)
	Total	Total	Total
Toxaemia	2 (3·3%)	9 (15·0%)	464 (17·8%)
Non-toxic separation of placenta	11 (18·3%)	5 (8·4%)	331 (12·7%)
Maternal illnesses	4 (6·7%)	2 (3·3%)	167 (6·4%)
Other	5 (8·3%)	4 (6·7%)	156 (6·0%)
Totals ..	22 (36·6%)	20 (33·4%)	1,118 (42·9%)

Toxaemia, perhaps the commonest known cause of prematurity, was only infrequently associated with kernicterus in the infant. Non-toxic separation of the placenta, on the other hand, occurred with rather unexpected frequency.

COMPLICATIONS OF LABOUR. Abnormalities of labour did not predispose to the development of kernicterus; the incidence of breech and forceps deliveries and other complications did not differ significantly in the three groups. It was not possible to assess accurately the incidence of asphyxia at birth, because the majority of the babies were delivered elsewhere, but a history of asphyxia was obtained in 28% (17) of the babies who developed kernicterus, and in 20% (12) of the controls.

POST-NATAL COMPLICATIONS. The complications listed in Table 9 were observed before any signs of

TABLE 9
POST-NATAL COMPLICATIONS

Complication	Babies with Complications	
	Kernicterus (60)	Controls (60)
Jaundice		
(*a*) present	59	28
(*b*) severe	38	2
Oedema	40	12
Atelectasis (marked degree) ..	35	19
Cyanotic attacks (after becoming a good colour) ..	34	12
Haemorrhages	9	1
(*a*) From mouth	—	1
(*b*) Melaena	8	—
(*c*) Purpura	1	—
Rectal temperature		
(*a*) On admission		
92° F. or below ..	12	4
100° F. or above ..	3	6
(*b*) Range during first three days		
3° F. or less	34	35
5° F. or more	8	7

kernicterus had appeared. Jaundice, oedema, atelectasis, cyanotic attacks, haemorrhages and hypothermia on admission were all more frequently observed in those who later developed kernicterus than in the controls.

Post-natal Treatment. The following factors having a possible bearing on the incidence of kernicterus were examined: the period of starvation before feeds were introduced, the administration of oxygen, of sedatives, and of vitamin B, C and K (Table 10).

PERIOD OF STARVATION. On average, feeds were introduced no later in the children who developed kernicterus than in the controls; the former were offered their first feeds after an average of 2·1, and the latter after an average of 2·0 days. Three children who developed kernicterus were, however,

TABLE 10
POST-NATAL TREATMENT

Treatment	Kernicterus (60)	Controls (60)
Starvation period (died before fed)	(2)	(7)
Less than one day	—	1
1 day	15	14
2 days	25	24
3 days	15	14
4 days	3	—
Vitamins B and C (daily from first day of feeding)	See above for first day feeding	See above for first day feeding
Vitamin K (total dosage):		
10 mg.	1 (outside case)	1 (died early)
20 mg.	1	5
30 mg.	10	14
40 mg.	21	25
50 mg.	14	13
60 mg.	6	2
Over 60 mg.	7	—
Sedatives (given before onset of signs)	9	6
Administration of oxygen (before onset of signs)	42	27

not given their first feed until the fourth day, a longer period of starvation than that experienced by any of the controls.

OXYGEN. Forty-two of the babies who developed kernicterus were given oxygen compared with only 27 of the controls. Oxygen is never given as routine treatment, but only when specifically indicated.

SEDATIVES. Before the onset of signs of kernicterus, nine affected babies and only six controls required sedatives (chloral or paraldehyde). Most babies who developed kernicterus had no sedation.

VITAMINS. The administration of vitamins B and C did not differ in the two groups. The administration of vitamin K did and was therefore studied in greater detail. All vitamin K was given in the form of 'synkavit'.

Only two of the controls, both fed late, were given more than 50 mg. of vitamin K, whereas 13 of the babies who later developed kernicterus were given more than 50 mg. These 13 babies were given extra vitamin K for the following reasons: haemorrhagic diathesis (nine), suspected intracranial haemorrhage (two) and delay in the introduction of feeds (two).

To clarify the relationship between the administration of vitamin K and the development of kernicterus the yearly incidence of kernicterus in two of the units has been calculated for the period 1945-54 and has been correlated with the dosage scheme of vitamin K in use each year (Table 11). Until 1950 it was the practice in unit S to give only one injection of vitamin K (1-10 mg.) on admission; after this date 10 mg. were given for the first three days of life. During 1953 and 1954 vitamin K was given eight hourly to babies with a tendency to bleed or with signs of increased intracranial pressure. With the increase in dose of vitamin K, the incidence of kernicterus rose four-fold, from 1% to 4%, approximately, of all admissions. In unit C it has been the practice, since 1950, to give 10 mg. of vitamin daily until two days after the introduction of feeds. Babies in this unit have therefore been given, on average, 30-50 mg. of vitamin K. The incidence of kernicterus in this unit (2·8%) since 1950 has been slightly higher than in unit S (2·2%).

In the case of the twins, the twin receiving more vitamin K was more likely to develop kernicterus than the twin who received less. There were 11 pairs of twins in which both lived long enough to develop kernicterus. In only one instance did both develop kernicterus; both received 40 mg. of vitamin K. Where dosage of vitamin K differed it was always the twin who received more vitamin K who developed kernicterus, but in four instances both received the same dose of vitamin K and yet only one developed kernicterus. On average, the kernicteric twin received 52 mg. of vitamin K (range 30-120 mg.) whereas the unaffected received 30 mg. (range 10-40 mg.). One affected baby received the unusually large dose of 120 mg. of vitamin K; if this child and its twin are removed from the series

TABLE 11
KERNICTERUS AND VITAMIN K DOSAGE

Year	Unit S.				Unit C.			
	Vitamin K (total mg.)	Admissions	Kernicterus		Vitamin K (total mg.)	Admissions	Kernicterus	
			Total	%			Total	%
1945	1–2	215	2	0·9				
1946	1–2	234	5	2·1				
1947	1–2	254	2	0·8				
1948	1–2	219	1	0·5	1–5	70	0	0
1949	10	243	4	1·6	1–5	141	0	0
1950	30	252	3	1·2	30–50	138	4	2·9
1951	30	269	3	1·1	30–50	164	3	1·8
1952	30	263	1	0·4	30–50	153	6	3·9
1953	30+	316	13	4·1	30–50	146	5	3·4
1954	30+	334	12	3·6	30–50	173	4	2·3

the kernicterus babies still received more vitamin K (average 44 mg., range 30-60 mg.) than the unaffected (average 31 mg., range 10-40 mg.).

Blood Group Incompatibilities. The incidence of the A, B, O groups and the C, D, E, c and d antigens were studied in the mother, father and child of the second group of patients. Data were not complete in every case, but they were in the majority. The distribution of the A, B and O groups is shown in Table 12. Although there is a slight, but not significant, excess of group O among the mothers, there is no appreciable diminution of group O among either the fathers or the affected children. Not all the affected children were less than 2,500 g. at birth, and were, therefore, not strictly speaking, premature, but if the 15 who weighed more than 2,500 g. at birth are removed from the series, the distribution of the ABO group is not materially altered. It is concluded that ABO incompatibility did not play a significant part in the production of kernicterus in this group.

TABLE 12
KERNICTERUS AND ABO DISTRIBUTION

	Percentage Distribution of ABO Groups			
	Parents and Kernicteric Child			
	Father	Mother	Child	Normal
O	44	50	46	44·3
A	50	39·5	45	42·8
B	4·5	7	6·5	9·1
AB	1·5	3·5	2·5	3·7
Cases	68	86	76	

It was considered unlikely that the less antigenic Rh antigens would predispose to the development of kernicterus in these cases; nevertheless, the distribution in the parents and children of the D, dd, C, c and E antigens was investigated (Table 13). The distribution did not differ from the expected to any significant degree. It is concluded that these factors played no part in producing kernicterus.

TABLE 13
KERNICTERUS AND DISTRIBUTION OF Rh FACTORS

	Percentage Distribution of D, dd, C, E, and c Factors			
	Parents and Kernicteric Child			
	Father	Mother	Child	Normal
D	83	85	80	85
dd	17	15	20	15
C	71	70·8	61	67·8
E	30·7	29·2	26	27·7
c	72·5	72·3	85	81·4
Cases	62	72	54	

Bilirubin Levels in Babies with Kernicterus and in Normal Full-term and Premature Babies. *Bilirubin levels were studied in 12 babies who developed kernicterus; in 10 the levels rose above 18 mg. per 100 ml. and in two they did not; these two were moribund when the estimations were made, and the levels may not indicate the heights to which the serum bilirubin had risen when kernicterus developed.

Serum bilirubin levels were also studied in 46 full-term and in 47 premature babies so that a clearer understanding of the levels in unaffected babies might be obtained (Fig. 1). In none did the serum bilirubin rise above 18 mg. per 100 ml. It is seen that the less the baby's weight at birth, the higher the post-natal bilirubinaemia and the later the peak. In babies weighing less than 2,000 g. at birth, the serum bilirubin is still rising on the sixth day of life, the day when kernicterus most commonly develops.

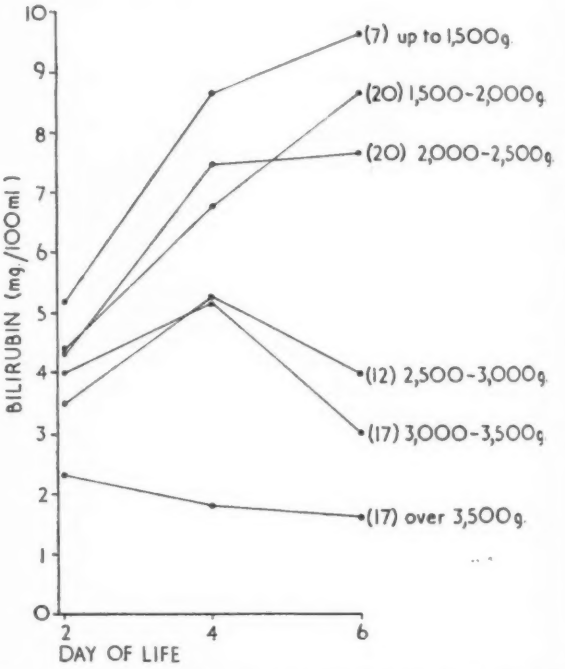

FIG. 1.—Mean bilirubin levels (indirect reacting) in 47 full-term and 46 premature babies. Since Fig. 1 was submitted comparative studies have been done on premature babies who received no vitamin K. and show generally lower curves for each weight group.

It appeared from these findings that all babies

* The figures given in this paper refer only to indirect reacting bilirubin.

with a serum bilirubin level above 18 mg. per 100 ml. developed kernicterus. This has, however, not been borne out by subsequent studies which are still in progress. To date, six premature babies have been encountered who did not develop kernicterus but in whom the serum bilirubin rose above 18 mg. per 100 ml.; nevertheless, 66% of those in whom the serum bilirubin rose above 18 mg. per 100 ml. have developed kernicterus.

Discussion

Although kernicterus has only recently been observed to be a hazard of prematurity, we do not think that it is necessarily a new disease in prematures, and this for two reasons. First, we have seen children with choreo-athetosis and a perceptive deafness who were deeply jaundiced in infancy, who were born prematurely and in whom no evidence of either Rh isoimmunization or of ABO incompatibility between the child and mother was found. Some of these probably had kernicterus of prematurity. Similar cases are to be found in surveys of children with cerebral palsy (Asher and Schonell, 1950). Secondly, we have noticed, over a number of years, a small group of prematures who survive the first few critical hours of life only to die unexpectedly towards the end of the first week. These children in the past were labelled 'late cerebrals'. Since 1945, necropsies have been performed by Dr. H. S. Baar on the majority of the premature babies in these units; it is only since 1945 that kernicterus has been recognized in this group of cases (Baar, 1945). The first few were diagnosed at necropsy; the majority are now diagnosed before death, and confirmed at necropsy.

To suggest that the disease is not new does not imply that its incidence may not have increased. With the greater care now devoted to prematures it is possible that more survive long enough to develop kernicterus. In addition, the introduction of new methods of treatment, e.g., vitamin K for haemorrhagic disease in the newborn, may have led unwittingly to an increase in its incidence. It is, nevertheless, not encountered frequently. The highest yearly incidence in any of the premature baby units in Birmingham was 4·1% of all admissions, and this unit admits routinely only the more immature prematures, those weighing less than 2,000 g. at birth. It has been found in only 6% of prematures at necropsy; its incidence in survivors has been very much less, namely 0·8%.

The most important predisposing factor appears to be immaturity, as evidenced by the weight of the baby at birth, and by the period of gestation, because the incidence of the disorder increases considerably as birth weight and period of gestation decrease; it is ten times more common, for example, in prematures delivered before the 30th week than in those delivered after the 36th. The higher incidence of the disease in males also underlines the importance of immaturity, for of two babies with the same weight at birth, the male is the more immature. (The female weighs less on average than the male at corresponding periods of gestation.) The rarity with which the disease, in our practice, is associated with toxaemia in the mother also confirms the importance of immaturity, for though babies of toxaemic mothers tend to be underweight and often marasmic, they are relatively mature, the majority being delivered after the 36th week, when, as we have already shown, kernicterus is unusual.

Although immaturity seems the most important predisposing factor, some post-natal conditions are encountered more frequently in babies later developing kernicterus than in controls (Table 9), e.g., jaundice, marked atelectasis, cyanotic attacks, haemorrhagic diatheses, subnormal temperatures and asphyxia at birth. It is possible that these complications may contribute to the development of kernicterus; on the other hand they may only be other evidence of immaturity.

Govan and Scott (1953) have suggested that the prime cause of the cerebral damage in prematures with kernicterus is anoxia, and that this occurs at birth. An analysis of our material also suggests that anoxia may be a predisposing factor, but the anoxia in our cases was not always due to asphyxia at the time of delivery; in some it was ante-partum, due to premature separation of the placenta, while in others it was post-natal and due to marked atelectasis. Our finding that the second of the twins was more frequently affected than the first also suggests that asphyxia may play a part. Anoxia, however, was not invariable.

In haemolytic disease of the newborn, the incidence of kernicterus has been shown to be related to the level of serum bilirubin. Hsia, Allen, Gellis and Diamond (1952), estimating the total serum bilirubin, not merely the indirect reacting, found that kernicterus commonly occurred when the serum bilirubin rose above 30 mg. %, but that it did not do so if the serum bilirubin was kept below 20 mg. % (Hsia, 1954). Our studies in prematures also show that kernicterus occurs most commonly when the serum bilirubin rises to unusually high levels, even though there is not a critical level above which all babies develop kernicterus. This being so, it is reasonable to assume that any condition which interferes with liver function (and it

is possible that anoxia and infection may do this), or which increases red cell destruction, will tend, if liver function is already immature, to cause a rise in the indirect reacting serum bilirubin, and, *pari passu*, in the incidence of kernicterus.

Allison (1955) has recently shown that vitamin K, in the form of 'synkavit', if given intramuscularly to vitamin E-deficient rats, will cause a severe haemolytic anaemia. Moore and Sharman (1955) have confirmed his findings and have also noted that different vitamin K analogues have, in this respect, varying degrees of toxicity; 'synkavit', the preparation used in the premature units under investigation in Birmingham, was found by them to be toxic. That 'synkavit' may be a precipitating factor is also suggested by the experience of Laurance (1955). A review of our practice tends to confirm this, for the incidence of kernicterus has been consistently higher in unit C, which has used a consistently higher dosage. The incidence rose fourfold in unit S when the dose of vitamin K was increased in 1953. In both units, when one of twins developed kernicterus it was always the twin who had received more vitamin K who developed this complication. On the other hand, and this suggests that vitamin K therapy is not of over-riding importance, in four instances both twins were given the same amount of vitamin K and yet only one twin developed kernicterus (the weights, on average of the twins, affected and unaffected, were the same). Moreover, no indirect evidence of any haemolytic process has been obtained as might have been expected had vitamin K caused a haemolysis; the babies who developed kernicterus were not anaemic when they developed kernicterus, and in only two of the survivors did the haemoglobin eventually fall below 8·6 g. %. Nevertheless, it is possible that vitamin K contributes to the development of kernicterus, and in our units the dose is now restricted to one injection on the first day of life, as this has been shown to be adequate for the prevention of haemorrhagic disease (Gordon, 1949). This alteration in treatment has not eradicated kernicterus; one baby who was given only 2 mg. of 'synkavit' and another who received none have subsequently developed kernicterus.

Hepatic immaturity would appear to be the most important underlying factor in the development of kernicterus in prematures. Liver function is so immature in these babies that the indirect-reacting bilirubin accumulates in the blood, rising to dangerously high levels. It is possible that substitution therapy with a suitable liver extract might enable the liver to metabolize and excrete bilirubin more efficiently, but, in the light of our present knowledge the only certain way of eliminating kernicterus in prematures would appear to be by an exchange transfusion whenever the bilirubin threatens to reach the danger level; by this means the indirect-reacting bilirubin is removed from the body at a time when the liver is unable to do this on its own account.

Summary and Conclusions

Details have been given of the mode of onset, mortality and signs in survivors of 60 babies developing kernicterus associated with prematurity only.

Ante-natal, natal and post-natal factors which might have contributed to the development of kernicterus in these cases have been analysed, and a comparison has been made with 60 controls and with all premature babies admitted to the units under investigation.

Bilirubin levels have been studied in 12 premature babies with kernicterus and in a series of normals.

The incidence of kernicterus and its mortality were greatest in those who were most immature at birth, as evidenced by the birth weight and period of gestation.

The post-natal bilirubinaemia was also greatest in the babies who were most immature, as evidenced by the weight at birth.

In 10 of 12 babies with kernicterus bilirubin levels rose above 18 mg. %. Levels of this order were uncommon in unaffected prematures, but they were encountered in six instances.

A history of anoxia and of excessive therapy with vitamin K ('synkavit') was more common in babies developing kernicterus than in controls, and may have contributed to the development of this complication, but the most important underlying aetiological factor appeared to be the immaturity of the infant, and, more particularly, the immaturity of the liver.

We are very grateful to Dr. H. S. Baar for his help and advice, and for his post-mortem studies; to Dr. W. Weiner for the serological studies; to Dr. A. H. Henley for technical assistance; and to the sisters and nursing staff of the premature baby units, without whose help this work could not have been undertaken.

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HYPOPROTHROMBINAEMIA IN THE NEWBORN

BY

A. S. DOUGLAS and P. DAVIES

From the United Oxford Hospitals

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In 1935 Quick introduced the one-stage 'prothrombin' test for the quantitative assay of prothrombin (Quick, 1935). It is now realized that a prolonged one-stage clotting time, using this test, can be due to deficiencies not only of prothrombin but also of two other plasma coagulation factors known as Factor V and Factor VII. Factor V was discovered by Owren as the result of investigation of a case of haemorrhagic disease with a prolonged one-stage clotting time, which was not due to a deficiency of prothrombin—the precursor of thrombin (Owren, 1947). The term Factor VII was introduced by Koller, Loeliger and Duckert (1951). Factor VII is important because its deficiency is the main factor which controls the prolonged one-stage 'prothrombin' time resulting from the administration of the coumarin drugs. It was the object of the present investigation to determine factors which control the one-stage clotting time in newborn infants.

Material and Methods

Collection of Plasma. Venous blood was collected into a graduated centrifuge tube and mixed with 3·8% sodium citrate in the proportion of 9 parts of blood and 1 part of citrate.

Reagents. The reagents—human brain thromboplastin, M/40 calcium chloride, human thrombin, human 'prothrombin', human fibrinogen and aluminium hydroxide Cα—were prepared by the methods described by Biggs and Macfarlane (1953).

Methods. Quick's one-stage 'prothrombin' time and related saline dilution curve were described by Biggs and Macfarlane (1953). The percentage is read from the saline dilution curve. The preparation of the thrombin-fibrinogen dilution curve is described by Biggs (1951). The two-stage area method of Biggs and Douglas (1953) was used for the measurement of prothrombin.

ESTIMATION OF FACTOR V. Factor V was estimated (*a*) by the activation of 'purified' prothrombin, a modification of the method of McClaughry and Seegers (1950) and is described by Douglas and Biggs (1953); (*b*) by the ability to correct stored normal oxalated plasma.

When oxalated plasma is stored the Factor V is labile and the one-stage clotting time lengthens. The ability of infants' plasma to correct this prolonged one-stage clotting time was tested by using 50% mixtures and compared with the property in this respect of fresh citrated normal plasma.

ESTIMATION OF FACTOR VII. This was estimated by the method described by Biggs and Macfarlane (1953). The principle of this is that 'tromexan' plasma is not usually sufficiently deficient in prothrombin significantly to affect the one-stage clotting time (Douglas, 1955). Mixtures of normal and 'tromexan' plasmas are made, and the one-stage clotting times performed on the mixtures. When these clotting times are plotted against the reciprocal of the concentration of Factor VII, a straight line relationship can be established if allowance is made for the residual Factor VII content of the 'tromexan' plasma. To test the Factor VII content of an infant's plasma 1 in 10 mixtures are made of infantile with 'tromexan' plasma and of normal with 'tromexan' plasma. The one-stage clotting times of the mixtures are then recorded.

Example. The following is a worked example:

Tromexan plasma .. .. = 44 sec.
1 part normal plasma in 9 parts 'tromexan' plasma .. .. = 21 sec.
1 part infant plasma in 9 parts 'tromexan' plasma .. .. = 38 sec.

Reading from a graph prepared as described:

44 sec. = 3%
21 sec. = 14·2%
38 sec. = 3·8%

Therefore the percentage Factor VII in an infant's plasma =

$$\frac{3\cdot8-3}{14\cdot2-3}\times 100$$

$$=\frac{0\cdot8}{11\cdot2}\times 100$$

$$=7\%.$$

ESTIMATION OF ANTITHROMBIN. This method is described by Douglas and Biggs (1953). The area method of prothrombin assay is applicable only when the normal and test specimens have the same antithrombin content. In three observations the curve of thrombin destruction by the infants was similar to the normal.

Healthy infants were examined. Specimens of cord blood were collected shortly after birth into a syringe by

venepuncture of the umbilical vein. Specimens of blood collected by dripping from the cut end of the cord almost invariably clot, probably due to admixture of tissue thromboplastin from the cord. At 48 to 72 hours after birth a further specimen was obtained by venepuncture of the antecubital veins, and on occasion of the external jugulars. It is inevitable that more specimens were collected than could be included in this investigation, many having to be excluded in account of clotting. A specimen of 1·8 ml. was collected into 0·2 ml. of 3·8 sodium citrate. This gave just sufficient plasma to be able to do Quick's one-stage test, the area two-stage test and the Factor VII content of each specimen. To half of the infants 10 mg. 'synkavit' were administered by intramuscular injection at the time of withdrawal of the cord blood.

Results

Factor V. The Factor V was estimated by the two methods described above.

(*a*) Four specimens of third-day infant blood were examined. The mean activation of the prothrombin under the influence of Factor V from these specimens is as good as that of the mean of the normals (Fig. 1).

(*b*) The correction of stored oxalated plasma is shown in Table 1.

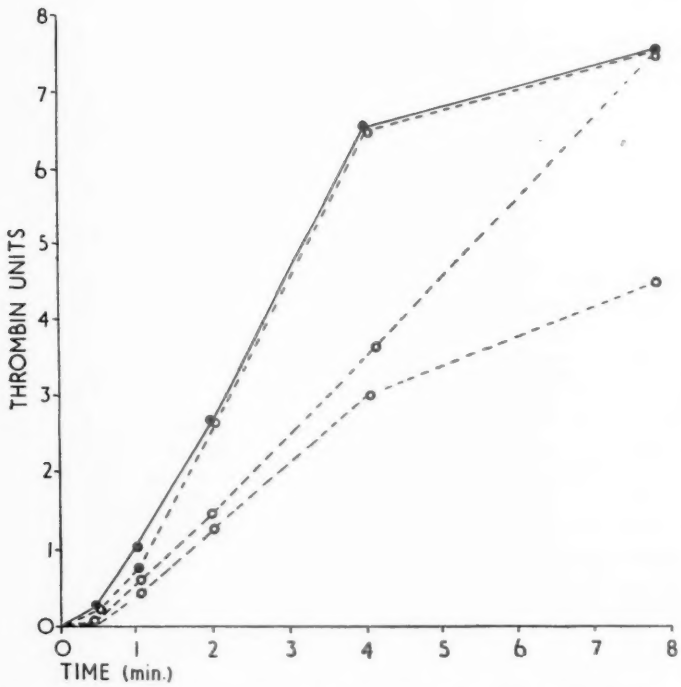

FIG. 1.—These curves represent the activation of purified prothrombin by Factor V. The discontinuous lines represent dilutions of normal (100%, 50%, 25%). The continuous line represents the findings in the mean of four observations on third-day infant bloods.

TABLE 1
CORRECTION OF STORED OXALATED PLASMA

Stored Plasma	+ ½ Normal Plasma	+ ½ Infant Plasma
21·8 sec.	15·7 sec.	16·7 sec.

(Mean of 7 observations.)

Factor VII and Prothrombin. Forty-two infants were examined. To 21 of these 10 mg. of vitamin K were given as described above. The mean of the results is shown in Fig. 2 and Table 2.

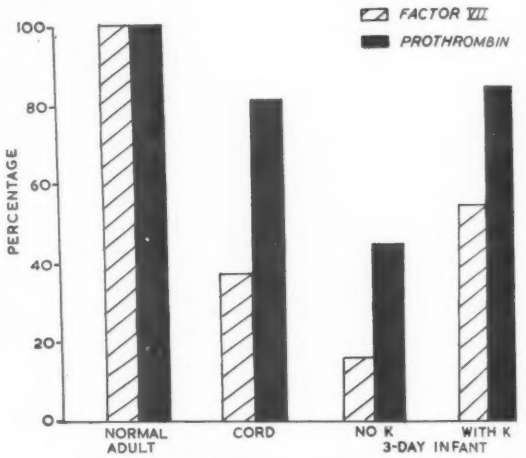

FIG. 2.—This histogram represents the level of Factor VII and prothrombin in the normal adult, and the cord blood (42 observations); also shown are the levels in the infant blood at the third day, when no vitamin K has been given and, when 10 mg. 'synkavit' have been administered intramuscularly shortly after birth.

TABLE 2
MEAN OF RESULTS FOR FACTOR VII AND PROTHROMBIN

	Normal	Cord	3rd Day No Vitamin K	3rd Day with Vitamin K
Factor VII	100%	38%	15%	54%
Prothrombin	100%	82%	44%	85%
Quick's one-stage test	100%	49%	12%	42%

There is a reduced level of both Factor VII and prothrombin in the cord blood. These levels fall considerably further at the third day. If vitamin K is given it fails to produce normal content of these factors on the third day, but it maintains levels at least as good as in the cord blood. In Figs. 3 and 4 the means of the observations on the two-stage test are shown.

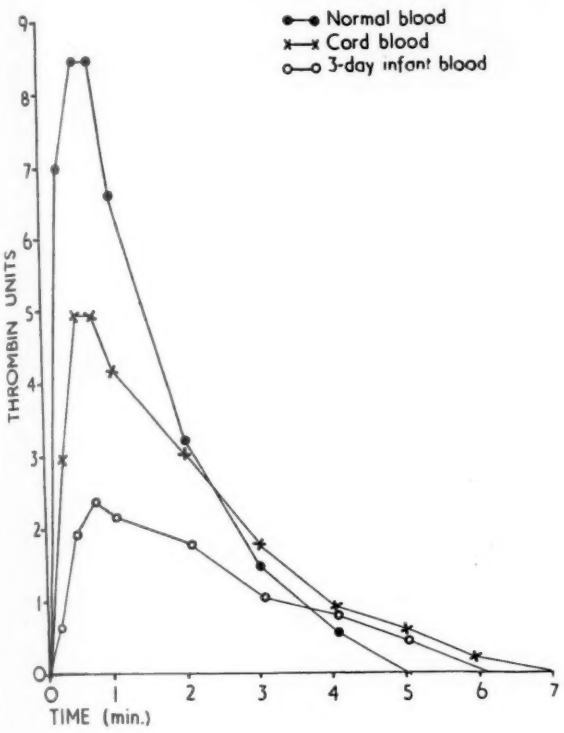

FIG. 3.—These curves represent the results of the two-stage test on the normal, the cord blood, and the third-day infant blood when no vitamin K has been given. The mean of the observations is represented.

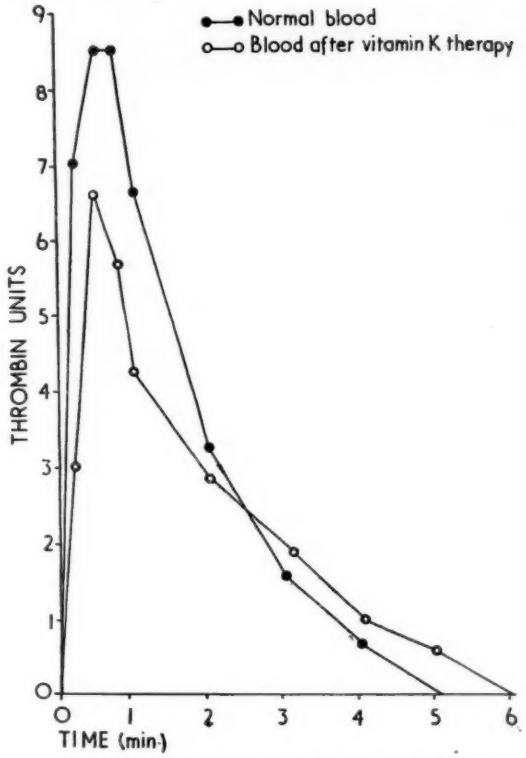

FIG. 4.—These curves represent the results of the two-stage test on the normal and the third-day infant blood when vitamin K has been given. The mean of the observations is represented.

Discussion and Conclusions

From these results it may be concluded that the 'hypoprothrombinaemia' of the newborn is due to a deficiency of both Factor VII and prothrombin. It is probable that the deficiency in Factor VII is the cause of the prolonged one-stage clotting time, since the degree of prothrombin deficiency observed is not sufficient to be likely to cause lengthening of the one-stage time (Biggs and Douglas, 1953). The degree of deficiency of these factors is much greater on the third day than it is in the cord bloods. The administration of water-soluble vitamin K to the infant prevents the fall in Factor VII and prothrombin, but does not restore these factors to normal levels.

Loeliger and Koller (1952) have also investigated the Factor VII and prothrombin content of cord blood and concluded that both of these factors were deficient. They record much lower figures than were found in this investigation (24% Factor VII and 28% prothrombin in a series of 33 cord bloods). The techniques employed by Loeliger and Koller are very different from those used in this investigation.

From the limited number of observations made in this study it is probable that there is no great deficiency of Factor V in the newborn. This confirms the findings of Stefanini (1951) who found 'the labile-factor activity only slightly depleted, whereas plasma prothrombin activity was much reduced during the third day after birth'. Stefanini was using a technique involving correction of the prolonged one-stage clotting time of stored oxalated plasma.

There has been some doubt thrown on the value of vitamin K in the prevention and management of haemorrhagic disease of the newborn. Hay, Hudson and Rodgers (1951) found that vitamin K administered to the mothers did not reduce the incidence of this disease. Sandford, Shmigelsky and Chapin (1942) found that vitamin K administered to the baby, or to the mother before birth, raised the prothrombin level but did not affect the frequency of haemorrhagic manifestations. It was not the object of this investigation to study the complete coagulation mechanism in the newborn nor to establish the relationship of vitamin K to the incidence and management of haemorrhagic disease of the newborn. It may well be that the coagulation

defect is more extensive than deficiency of Factor VII and prothrombin. Biggs and Macfarlane (1953) have shown that the thrombin-fibrinogen reaction is abnormal in the newborn. Douglas (1954) has shown that the serum from an infant with haemorrhagic disease of the newborn was defective in its ability to form intrinsic thromboplastin. Haemorrhage in the newborn may be due to abnormalities other than those associated with a prolongation of the one-stage clotting time; for example, thrombocytopenia of the newborn is a well-recognized entity.

This investigation presents reasonable evidence that the administration of vitamin K to the newborn infant arrests the usual fall in both Factor VII and prothrombin. Even if deficiency of Factor VII and prothrombin proves ultimately to be only a contributory factor in haemorrhagic disease of the newborn, it is of importance to know that vitamin K does control the level of these substances.

Summary

The 'hypoprothrombinaemia' of the newborn is due to a deficiency both of Factor VII and prothrombin. Water-soluble vitamin K given to the infant, though not producing normal levels of these coagulation factors, prevents the deficiency which is normally present on the third day.

We wish to thank Dr. R. G. Macfarlane, Dr. Rosemary Biggs and Dr. V. Smallpeice for their guidance and interest in this investigation. One of us (A.S.D.) wishes to thank the Medical Research Council for a fellowship in clinical research, enabling him to carry out this work.

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POTASSIUM LEVELS IN EXCHANGE TRANSFUSION*

BY

W. A. B. CAMPBELL

From the Royal Maternity Hospital, Belfast

(RECEIVED FOR PUBLICATION JUNE 9, 1955)

In the Royal Maternity Hospital, Belfast, in common with other centres treating haemolytic disease of the newborn, the number of infants requiring exchange transfusion has been increasing steadily in the past few years. In 1950 there were seven live-born affected infants, of whom five were treated, all successfully, by exchange transfusion, in 1954 there were 42 live-born affected infants of whom 34 were treated by exchange transfusion, 31 surviving.

At the end of 1952 and the beginning of 1953 there were two deaths during the actual transfusion in infants who were comparatively mildly affected. The deaths were sudden and unexpected, and it occurred to us that they might have resulted from an excess of potassium in the bottles of blood used for the exchange. The plasma from several random bottles was therefore analysed, and it was found that levels of 40 mg. % were not uncommon, even though none of the blood had been more than one week in store.

In an attempt to determine whether hyperpotassaemia might in fact be the cause of death in these infants, an investigation was planned on the following lines:—

In every case where it was decided to treat the baby by exchange transfusion, samples of blood were taken from the umbilical vein at the beginning of the tranfusion and after every 100 ml. of the exchange. These samples were taken into heparinized tubes and the plasma separated within four hours. Similar samples were taken from the bottles of stored blood used for the exchange. In general, the criteria for transfusion were those suggested by Mollison (1952), and an exchange of 60 ml. of packed cells per lb. weight was aimed at.

When data had been obtained from 20 infants (21 transfusions) they were examined; the potassium levels for this control group are shown in Fig. 1. It will be seen that 13 of the 104 samples had potassium levels of 28 mg. % or above, and that three of the four deaths in this group had potassium levels above 32 mg. %. (The fourth death was of a premature infant, weighing 4 lb. 6 oz., with a cord blood haemoglobin of 42% (6·2 g.).)

To attempt to correlate the potassium level in the bottles used with the levels reached in the infants, the cases were grouped according to the greatest level in the bottles used, and the maximum level in the babies charted. These results are shown in Table 1.

TABLE 1

POTASSIUM LEVELS (mg. per 100 ml.) IN CONTROL GROUP

Maximum in Bottle	Mean in Bottle	Maximum in Child						Mean of Maximum Levels in Children
		−20	−24	−28	−32	−36	−40	
Below 26	22·34	1	2	1*	2	1*	—	25·83
26–32 ..	29·66	1	1	3	—	—	1*	26·3
Over 32	45·3	1	3	2	1	1*	—	25·95

* Indicates deaths.

In such a group of cases, with many variable factors such as birth weight, cord blood haemoglobin, birth order, maturity, etc., it is impossible to make any valid statistical analysis. It does not appear, however, from the figures shown in this table that there is any simple relation between the potassium level in the bottle of blood used for exchange and the maximum level reached in the child. In this we were unable to confirm the work of Miller, McCord, Joos and Clausen (1952), who found that in a small series of eight cases there was a direct relation between the potassium level in the stored blood and that reached in the child.

Although the results obtained in this control group do not prove that the high potassium levels were the actual cause of death, rather than a coincidental result of some other process in the disease itself or the transfusion, it was felt that an attempt should be made to guard against the rise. It is generally accepted that the most rapid way to remove potassium from the extracellular to the intracellular fluid is to give glucose and insulin

* Based on a paper read to the Ulster Paediatric Society on May 7, 1955.

intravenously. In the absence of any previous reports on this technique as applied to the newborn infant, it was decided in the first instance to give 2 g. of glucose and 2 units of insulin into the umbilical vein after the first 100 ml. of blood had been exchanged. When the first few transfusions had been carried out it was found that the blood sugar levels were high, and as the 50% glucose used tended to make the syringe sticky and thus added slightly to the technical difficulty, it was decided to give the insulin alone. (It should be mentioned that the standard anticoagulant solution used by the Northern Ireland Blood Transfusion Service contains glucose, so that the plasma glucose level of stored blood is generally about 700-800 mg. per 100 ml.)

The potassium levels from 16 infants (17 transfusions) are shown in Fig. 2.

It will be seen that the general trend is lower in this ' insulin' group than in the 'control' group.

The only death in this treated series was a 6-lb. baby with very intense jaundice, who died during a second transfusion, with clinical evidence of kernicterus. (Consent was unfortunately not obtained for a necropsy.) The group of six rather high readings (32 mg. per 100 ml. and above) was examined to see whether any reason could be found for the apparent failure to respond to the insulin. One was the specimen only 100 ml. after giving the insulin, the subsequent samples having normal values, and the infant showing no clinical sign of distress. It is possible that in this case even higher and perhaps fatal potassium levels might have occurred had insulin not been given.

Two were the samples at the end of transfusion in infants showing some collapse, not sufficient to cut short the exchange, and the remaining three were from the one infant, who had intense jaundice and who died at the age of 2 months with evidence of kernicterus.

For comparison with the control group, the relation between the potassium levels in the bottles

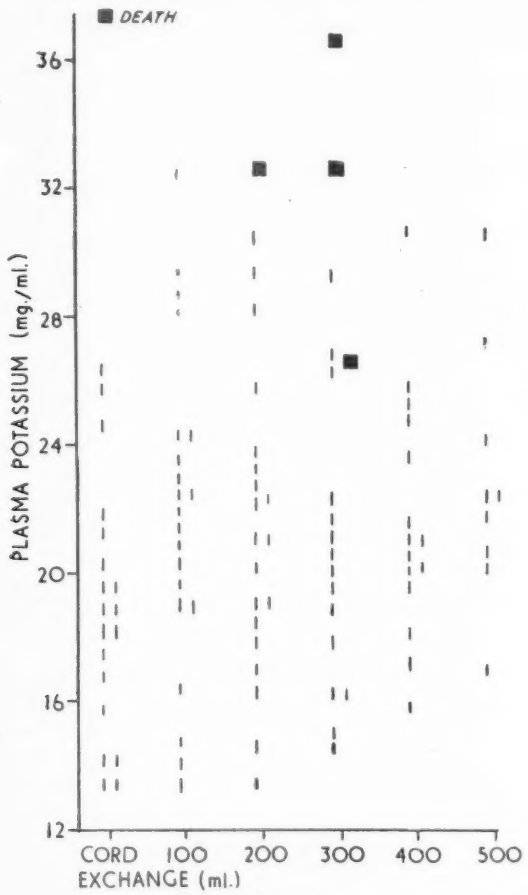

FIG. 1.—Control group.

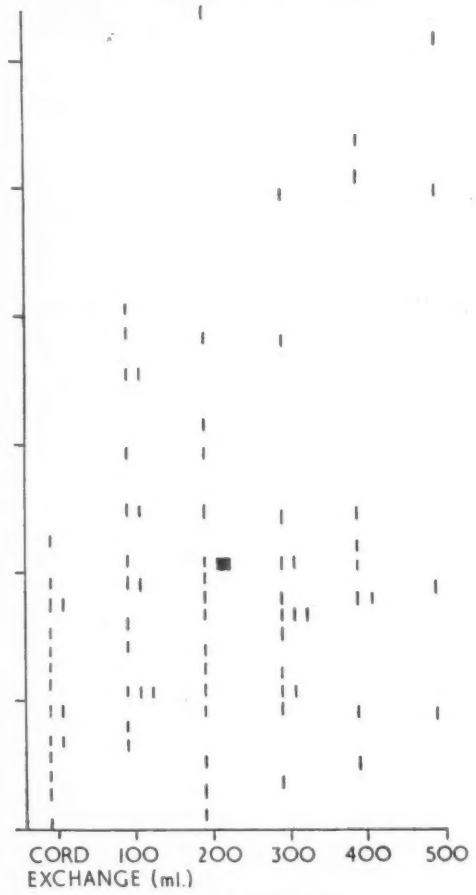

FIG. 2.—Insulin group.

used and the maximum levels reached in the infants is shown in Table 2. This shows little difference from Table 1.

TABLE 2

POTASSIUM LEVELS (mg. per 100 ml.) IN INSULIN GROUP

Maximum in Bottle	Mean in Bottle	Maximum in Child						Mean of Maximum Levels in Children
		−20	−24	−28	−32	−36	−40	
Below 26	23·48	2	3	2	—	—	—	21·91
26–32 ..	29·94	3	—	1*	1	—	2	26·6
Over 32	36·86	1	—	1	—	—	1	27·66

* Indicates deaths.

In such small groups of cases, with many variable factors in the individual infants, one cannot make any detailed statistical analysis. Table 3 shows that

TABLE 3

COMPARISON OF CONTROL AND INSULIN GROUPS

	Infants	Transfusions	Mean Birth Weight (oz.)	Mean Cord Haemoglobin (%)	Deaths
Control	20	21	115·6	81·4	4
Insulin	16	17	105·8	81·8	1

as far as birth weight and cord blood haemoglobin were concerned there was no great difference between the two groups.

The actual mean levels of potassium at each stage of the transfusions are shown in Table 4. These are of much less practical importance than the individual readings shown in Figs. 1 and 2, since the occasional high value, associated clinically with collapse or death, does not make an appreciable difference to the mean reading. The mean blood sugar levels are also shown in Table 4, and also the

TABLE 4

MEAN ELECTROLYTE VALUES (mg. per 100 ml.)

		Cord	100	200	300	400	500
Control ..	Potassium	18·6	21·7	21·8	22·4	21·7	22·8
Insulin ..	Potassium	16·4	20·6	20·0	20·0	22·2	25·6
Insulin ..	Sugar	55·0	109	227	252	237	180
Normal infants ..	Potassium	21·4					

mean cord blood potassium in a series of 16 normal infants. The latter was found to agree with the value given by Earle, Bakwin and Hirsch (1951) and not with the much higher values quoted by Smith (1951).

Discussion

From the results obtained in this investigation it appears that hyperpotassaemia is not infrequent in the course of exchange transfusions for haemolytic disease of the newborn, and that the levels reached are potentially lethal. As has been stated, there is no proof that the high potassium content of the plasma has been the cause of death in those infants who died suddenly rather than a coincidental finding. Little work appears to have been done on this aspect of exchange transfusion; apart from a passing reference to one fatal case by Walker and Neligan (1955), the only article that I have been able to trace is that of Miller *et al.* (1952) already referred to. They relate the high potassium levels directly to the high content of the transfusion blood; our results do not confirm this, but it is difficult to offer any explanation for the apparent individual variation in the rate of accumulation of potassium. Although the series is too small to justify detailed subdivision into subgroups according to all the variable factors involved, there does not seem to have been any relation to the severity of the disease as measured by cord blood haemoglobin or bilirubin levels. As far as possible the actual technique of transfusion has been standardized to eliminate possible variations in such factors as rate of exchange, chilling of the baby, etc.

Gustafson (1951) has reported electrocardiographic changes suggesting hypocalcaemia during exchange transfusion, although the total calcium content of the blood did not show any significant change. The plasma calcium levels were estimated in the first few of our series, but as there was no apparent variation, this was discontinued and attention concentrated on the more striking potassium changes. We hope to be able to obtain a direct-reading electrocardiograph in order that a continual check may be kept on the action of the heart muscle during transfusion, as this may prove to be the most sensitive estimate of electrolyte changes and may show the need for appropriate treatment before serious harm can occur.

Our present opinion is that there is sufficient evidence to support the theory that hyperpotassaemia is a cause of death to justify the routine use of insulin in future transfusions. It might be advisable to give a slightly larger dose, e.g., 3 units, before giving the first 10 ml. replacement. (In this connexion, it has been found that a tuberculin syringe is essential for accurate measurement of dosage.)

It will necessarily take a year or more to obtain a really large series of cases, but it is hoped that other centres may consider similar investigations as a check on our findings.

Summary

An investigation has been carried out into the plasma potassium levels in newborn infants undergoing exchange transfusions for haemolytic disease.

Toxic levels have been found in some infants, and it is suggested that this may be one factor in causing death. The potassium level in the child does not appear to bear a direct relationship to that in the stored blood used.

Intravenous insulin has been used in an attempt to reduce the potassium levels, with some success.

I am very grateful to my obstetric and paediatric colleagues in the Royal Maternity Hospital, Belfast, for much help both in planning and carrying out this trial. Mr. D. W. Neill, M.Sc., A.R.I.C., Senior Scientific Officer, Belfast Hospital Group, has given invaluable advice and much practical assistance at every stage.

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PAROXYSMAL TACHYCARDIA IN INFANCY

BY

JOHN APLEY, BERYL D. CORNER and THOMAS C. GIBSON

From the Department of Child Health, University of Bristol, and Bath Royal United Hospital

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There have been many reports of paroxysmal tachycardia as it occurs in adults, some describing it in children, but very few in which infants alone are considered. Yet, though diagnosis in infancy is most urgent, it is then least familiar; there must still be many cases misdiagnosed, for example, as pneumonia. In an outstanding paper Hubbard (1941) first drew attention to the clinical picture of paroxysmal tachycardia in infancy. He described nine personal cases, the largest individual series so far. In 1952 Nadas, Daeschner, Roth and Blumenthal incorporated Hubbard's and other cases, taking infants and children together, and making a total of 41 seen over a period of 20 years at the Boston Children's Hospital. Some valuable conclusions about differences between the two age groups were drawn. In this country, since Poynton and Wyllie (1926) reported a case of 'delirium cordis' in infancy, very few cases have been published (Leys, 1945; Neubauer, 1945; Wright, 1953). We present here a short account of 13 further cases of paroxysmal tachycardia in early infancy.

Clinical Picture

The case reports are tabulated. Further details are given in the three fatal cases.

General. The child's general condition was always, though variably, affected. He appeared unwell and listless; often he was feverish and restless and sleep was disturbed. Feeding was usually difficult, with unwillingness to feed or inability to continue feeding for more than a short time.

The temperature was raised in four of our cases. In two of these pneumonia was diagnosed, but in the remaining two (Cases 11 and 12) no infectious process was found either clinically or radiologically, and the rise in temperature was presumed to be due to heart failure. Case 12 developed a temperature of 104° (the highest in the series) which fell to normal in a few hours, at the same time as the heart rate and liver size returned to normal, on treatment only with 'digoxin'.

Respiratory. Superficially the most obvious disturbance appeared to be respiratory, and most infants had been diagnosed as suffering from pneumonia. In 11 of 13 cases respiration was markedly rapid and sometimes laboured, usually with rib recession and activity of accessory muscles of respiration. Moist sounds in the lungs were, however, detected in only four cases, and two of these were considered to be cases with pneumonia in addition to paroxysmal tachycardia. In these two infants radiography of the chest showed definite pneumonic changes. Congestion of the lung fields was suggested radiologically in half the cases.

Alimentary. In three infants vomiting occurred. In one of these the diagnosis of hypertrophic pyloric stenosis had been suggested; another was referred for an opinion as a feeding problem. One infant with pneumonia as well as paroxysmal tachycardia had diarrhoea.

Cardiovascular. In eight infants (including one with pneumonia) slight cyanosis was observed; four of them had an ashen colour, presumably due to associated pallor. Pallor was observed in two other infants who were not cyanosed. Dilatation of the neck veins could be detected in only one case, though it was looked for in all. In 11 cases the liver was greatly enlarged. Scrotal oedema occurred in one infant.

The size of the heart is difficult to ascertain by clinical methods in infants and in only two of our patients was the diagnostic point of cardiac enlargement made; radiologically the heart size was increased in three cases.

Clinical estimation of the heart rate was sometimes only an approximation, because of its extreme rapidity. We found that the rate could be fairly reliably determined by auscultation of the heart; estimations from the radial pulse, arteries in the neck, or superior sagittal sinus through the open fontanelle, were useless and often misleading. It is

TABLE

13 CASES OF INFANTILE PAROXYSMAL TACHYCARDIA

	Case	Sex	Birth Weight (lb. oz.)	Age at First Attack	Heart Rate in Attack	Other Signs in Attack	Persistence
Diagnosed in maternity units	No. 1 (M.B.)	F	5 15	6 days	260	Pallor, rib recession, rapid respiration, large liver	Died 11 days old; recurrences after initial improvement on digitalis
	No. 2 (G.D.)	F	7 2	10 days	210	Cyanosis, large liver, rapid respiration	Eight attacks in 16 months; none in next two years
	No. 3 (T.D.)	M	3 8	(? 3 days) 11 days	280	Pallor with cyanosis, large liver, rapid respiration, scrotal oedema	Attacks for 2 weeks; none in subsequent 3 years
	No. 4 (L.R.)	F	7 9	11 days	280	Pallor with cyanosis, respiratory distress	No further attacks in 2 years
	No. 5 (J.H.)	M	5 10	15 days	290	Pallor, cyanosis, large liver, rapid respiration	Occasional recurrences for 3 months; none in next 9
Sent into hospital	No. 6 (C.B.)	F	8 4	(? 4 days) 15 days)	240	Diarrhoea, alternating pulse, large liver, rapid respiration (80), pneumonia. Temp. 103°	Died 17 days old; on digitalis and antibiotics 1 day
	No. 7 (P.C.)	M	7 5	(?21 days) 24 days	280	Vomiting, cyanosis, large liver, rapid respiration, pulmonary crepitations	No recurrence in 3½ years
	No. 8 (C.R.)	M	7 10	(?27 days) 34 days	290	Diarrhoea, pallor and cyanosis, rapid respiration, large liver	No further attacks for 6 months
	No. 9 (P.T.)	M	7 15	35 days	250	Vomiting, large liver, rapid respiration. Temp. 99·6°	Several attacks first 6 months; then no recurrence in 1½ years
	No. 10 (L.H.)	F	8 8	42 days	240 clinically	Vomiting, pallor, neck stiffness, large liver	Relapses becoming less frequent during 6 years
	No. 11 (D.P.)	M	7 0	115 days	250	Cyanosis, rapid respiration, large liver, large heart. Temp. 101·2°	Died 116 days old; on 'digitalis' and antibiotics 1 day
	No. 12 (R.B.)	M	7 10	129 days	220	Cyanosis, fever, large liver, rapid respiration. Temp. 104°	One relapse in a few days, but no more for 2 years
	No. 13 (J.A.)	M	7 5	(Probably earlier attacks) 165 days	120 clinically 230 by E.C.G. 460 auricular rate by E.C.G.	Not thriving, large heart, pulmonary crepitations, respiratory infection	A few attacks until 7 months old; then no more in next 3 years

important to note that in one case (No. 6) pulsus alternans occurred at times; pulse estimations were then dangerously inaccurate, since the apparent rate was half the correct figure as obtained by auscultation over the heart. In some cases transient systolic murmurs were heard over the praecordium.

Electrocardiographic Findings

In 12 of our 13 cases electrocardiograms were recorded during an attack of tachycardia. The rates varied from 210 to 290. Case 13 was the only certain example of auricular flutter, with an auricular rate of 460 and a 2 : 1 ventricular response (Fig. 1).

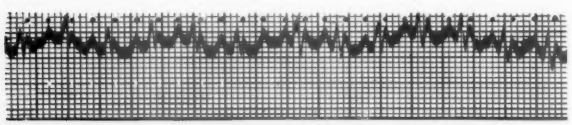

FIG. 1.—Case 13: E.C.G. lead I, showing 2 : 1 flutter with ventricular rate 230 and auricular rate 460. The auricular complexes are marked with dots.

We could clearly identify only one record as nodal in type (Case 9) with the P wave following the ventricular complex (Fig. 2). The remainder were classified as supraventricular tachycardia. There were no examples of ventricular tachycardia.

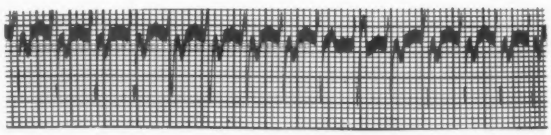

FIG. 2.—Case 9: E.C.G. lead I, illustrating low nodal tachycardia with P inversion immediately following Q.R.S. One upright P wave is seen, probably of sinus origin.

Electrocardiograms in normal rhythm were available. They were normal for infants of this age group, with one exception; immediately following attacks of paroxysmal tachycardia the P waves were often unusually tall, reaching 6 mm. on one instance (Case 9, lead II). This temporary anomaly has been previously noted by Nadas *et al.* (1952). In the only patient (Case 10), in whom an attack of tachycardia was not recorded, the electrocardiogram in normal rhythm was typical of the Woolf-Parkinson-White syndrome with short P-R interval and QRS suggesting left bundle branch block due to premature activation of the right ventricle (Fig. 3). In view of the history and typical clinical findings, including the clinical determination of a heart rate of 240 in several attacks, the diagnosis of paroxysmal tachycardia seemed reasonable. In another infant (Case 5) partial right bundle branch block and a shortened P-R interval (0·08 seconds) were recorded

following an attack. These did not persist and may have represented a transient form of the Woolf-Parkinson-White syndrome, since in the following electrocardiogram in normal rhythm the P-R interval was 0·10 seconds.

FIG. 3.—Case 10: E.C.G. leads I, II, III showing short P–R interval (0·08 seconds) and Q.R.S. suggesting left bundle branch block (Woolf-Parkinson-White syndrome).

Fatal Cases

There were three deaths in our series, and the clinical and necropsy findings are given in some detail.

Case 1. M.B., a girl, was born after a normal pregnancy and labour (birth weight 5 lb. 15 oz.). On the sixth day she refused feeds and abnormal respiration was observed, periods of hyperpnoea alternating with apnoea.

On examination she was a pale, limp child with cold extremities. The temperature was 98·0° F., the pulse rate 260 per minute. Respirations were irregular and rapid. Rib recession occurred, though there were no abnormal signs in the lungs. The cardiovascular system appeared normal apart from tachycardia. There was no hepatic enlargement or oedema.

An electrocardiogram showed 1 : 1 auricular tachycardia (rate 260), and no abnormality was found on a radiograph of the chest.

A diagnosis of paroxysmal tachycardia was made and 'digoxin', 0·025 mg., was given six hourly intramuscularly. The child was nursed in an oxygen tent. Within 24 hours the heart rate fell to 180 per minute and she improved considerably. The following day she appeared to relapse, becoming cyanosed and feeble, with evidence of respiratory distress. On the tenth day she again improved, heart and respiration rates were regular, and 'digoxin' was discontinued. On the eleventh day she suddenly became deeply cyanosed, cold and feeble with rapid irregular respirations and an extremely rapid and feeble heart beat. 'Digoxin' and oxygen were again administered, but six hours later she died.

NECROPSY REPORT. Dr. N. J. Brown reported as follows:

Slight generalized oedema was present with excess fluid in the abdominal and pleural cavities. There was a small amount of excess fluid in the pericardium. The heart did not appear enlarged. The right auricle and the ventricles were a little dilated; the left auricle and all valves were normal. The left ventricle showed an area of slightly thickened and opaque endocardium, measuring 9 × 5 mm., immediately below the aortic valve on the upper part of the posterior wall. At the lower end of this patch there was a small group of subendothelial petechial haemorrhages. A large haemorrhage, 18 × 2 mm., was found in the upper part of the interventricular septum, continuous with the subendocardial haemorrhages. Another small haemorrhage, 3 mm. in diameter, was visible beneath the epicardium in the immediate vicinity of the sino-auricular node on the lateral aspect of the junction of the superior vena cava with the right auricle.

The lungs showed patchy collapse but no infection. The liver (weight 137 g.) and the spleen (weight 17 g.) both showed acute venous congestion. There were no other significant findings.

HISTOLOGY OF THE HEART. The endocardium was slightly thickened and showed an increase in elastic tissue (Fig. 4). The myocardium showed a diffuse and

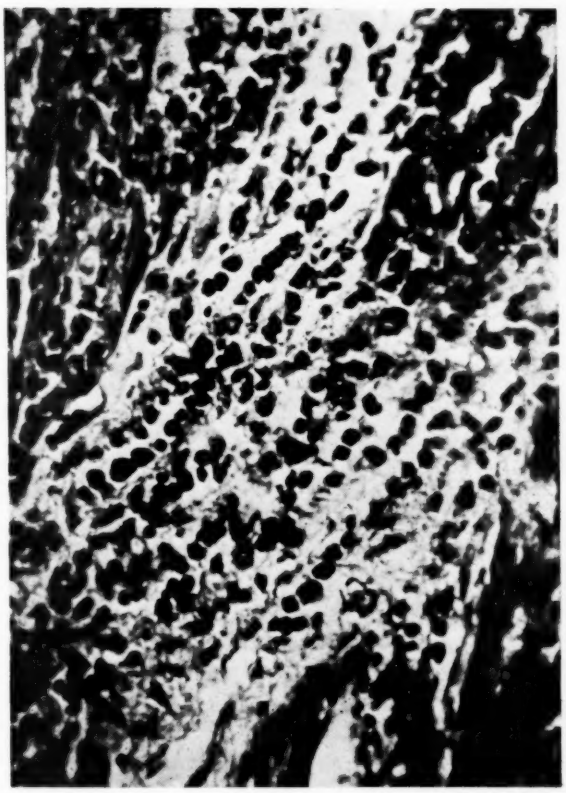

FIG. 4.—Case 1: photomicrograph of myocardium (× 400, haematoxylin and eosin), showing intense interstitial infiltration by mononuclear cells.

intense infiltration by large mononuclear cells and a few polymorphs; this reaction was not particularly noticeable round blood vessels. There were some strands of fibrous tissue traversing the myocardium but the muscle fibres themselves were normal.

COMMENT. This appeared to be a case of acute interstitial myocarditis. It is true that there was perhaps a little increase in fibrous and elastic tissue in the endocardium, but not to anything like the extent that is seen in typical fibro-elastosis. On the other hand myocarditis, although patchy, was well marked and not merely a reaction to haemorrhage. There was no evidence of toxoplasmosis nor could inclusion bodies be seen in the heart or other organs.

Case 6. C.B., a girl, was born after a normal pregnancy and labour (birth weight 8 lb. 4 oz.). On the fourth day there had been dyspnoea and grunting respirations. On the fifteenth day she was noted to be pale and cold, having refused feeds and passed green slimy stools. Respirations were stertorous, the temperature 97·4° F. She was treated with penicillin and a sulphonamide mixture. During the next two days the temperature rose to 103° F. and the respirations to 80.

On examination there were signs of consolidation at the right base and it was noted that the heart rate was unduly rapid at 240. At times the pulse seemed to halve its rate because alternate beats felt softer, but auscultation gave the true rate. The liver was palpable two fingerbreadths below the costal margin.

An electrocardiogram showed 1 : 1 auricular tachycardia, rate 240.

A radiograph of the chest showed cardiac enlargement and possible hilar congestion. There was pneumonitis in the right lower zone and a small left pleural effusion.

A diagnosis of paroxysmal tachycardia complicating pneumonia was made. 'Digoxin', 0·05 mg., was given intramuscularly and repeated in five hours. No improvement took place and she died within seven and a half hours.

NECROPSY REPORT. Dr. H. J. Heathcote reported as follows:

The body was that of a well covered infant, with the umbilicus healed over. The pleural, pericardial and peritoneal cavities contained a considerable quantity of fluid. There was a small area of partial collapse in the middle lobe of the right lung, with a small amount of pus in the bronchi of the right lower lobe. The lungs were congested and oedematous. The empty weight of the heart was 1 oz., and the right auricle was slightly dilated. The vessels, chambers and valves were normal; the foramen ovale was not patent. The liver was slightly enlarged, other abdominal organs normal.

COMMENT. It is possible that in this case the tachycardia was idiopathic, but in view of the pulmonary and other findings it has been included amongst those associated with infection.

Case 11. D.P., a boy, was born after a normal pregnancy and labour (birth weight 7 lb.). At three weeks he had coryza and pyrexia which was treated with sulphonamides. Since then he had gained weight slowly, and he was noted lately to have a pigeon chest. On the day of admission (115th day of life) he started screaming half an hour after the 2 p.m. feed and continued all afternoon. Respiration was noted to be rapid and grunting in quality; he felt hot, had a slight cough and was apathetic. He was admitted to hospital in the evening as a case of respiratory infection.

On examination he was cyanosed, with a temperature (rectal) of 101·2°, pulse rate at least 270 and respiratory rate 50 with reversal. The heart was clinically enlarged. The lungs were clear. The liver was enlarged to the umbilicus and later to the right iliac fossa. The ankles were oedematous.

An electrocardiogram showed 1 : 1 auricular tachycardia, rate 250.

A diagnosis of paroxysmal tachycardia was made and he was given 0·1 mg. of 'digoxin' by mouth, and 150,000 units of procaine penicillin intramuscularly. He was nursed in an oxygen tent. There was no improvement and within three hours he died.

NECROPSY REPORT. Dr. A. J. M. Reese reported as follows:—

There was a small amount of fluid in the abdominal cavity and in both pleural cavities. There were a few petechial haemorrhages on the pericardium. There was a thin layer of fibrin on the visceral pericardium of the ventricles. The heart weighed 115 g.; the right auricle was of normal size with a normal endocardium. The tricupsid valve was normal. The right ventricle was normal in size with a wall of normal thickness and a normal endocardium. The pulmonary valve and artery were normal. The foramen ovale was closed. The left auricle was dilated: the wall was thickened and there was a marked thickening and opacity of the endocardium. The mitral valve was narrowed with a ring 3·6 cm. in circumference. The chordae tendineae were not thickened but were short. The left ventricle was dilated. The wall was greatly hypertrophied and 1 cm. thick. The endocardium was dense and white and all the columnae carneae were white and fibrotic. The thickening extended almost up to to the aortic valve, but this structure was normal. The coronary arteries were normal. The aorta and great veins were normal. The left lung weighed 65 g. and was normal. The right lung weighed 90 g. and was solid and congested; it contained no air except for a few segments at the base. The liver weighed 185 g. and was congested. Otherwise no other abnormality was found.

HISTOLOGY. Section of the left ventricle showed gross fibro-elastosis spreading from the endocardium into the substance of the muscle. Fine elastic fibres were present deep in the myocardium. A section of the right lung showed severe congestion with blood in the alveolar spaces.

COMMENT. This was a case of heart failure due to severe fibro-elastosis confined to the left auricle and ventricle. The mitral valve was stenosed. There were no other malformations.

Treatment

During an Attack. Nadas *et al.* (1952) have reported a death following bilateral carotid pressure, and we consider that mechanical methods to induce reflex vagal stimulation should not be used, as they are unsatisfactory and potentially dangerous in infants.

Digitalis preparations have been found to be of value (Hubbard, 1941) and 'digoxin' was given in 11 of our cases. The optimum dosage of 'digoxin' approximated to 0·05 mg. initially for a 7 lb. infant, given either intramuscularly or orally, followed by 0·025 mg. six-hourly for the first 24 hours. Subsequently a proportionate maintenance dose should be given. Infants appear to tolerate digitalis well and no important side-effects were noted. It was our impression that 'digoxin' was effective in controlling cardiac failure rather than in terminating the paroxysms. This is of importance since failure has usually developed by the time the infant is seen.

In view of the dangers of cardiac failure, diagnosis and treatment should be attempted as early as possible. We were fortunate in that many of our cases were diagnosed while still in hospital, eight within 24 hours of the onset of symptoms and two within 48 hours. We could not, however, correlate early diagnosis with a quick response to treatment, possibly because diagnosis is likely to be made earlier in the more serious cases for the very fact that in them signs and symptoms quickly become evident.

The value of treatment directed towards terminating the paroxysm is less clear. Reports on the successful use of 'mecholyl' in three cases (Silverman and Werner, 1950; Gibson, 1950) are tempered by failure in five with one death due to cardiac arrest (Nadas *et al.*, 1952). We gave 'prostigmine' and 'amechol' each on one occasion, without effect. Because they are not very effective, and are potentially dangerous, it is questionable whether the cholinergic drugs should be used in infants except as a last resort.

Procaine amide was used in one case (Case 5), 17·5 mg. being given intravenously over a period of eight minutes under continuous electrocardiographic control. No change in rate or rhythm was noted. Sher (1953) has, however, given up to 100 mg. of procaine amide intravenously to an 8-week-old infant with immediate termination of an attack and no side-effects. Quinidine was not given to our cases, as knowledge of its effects in infancy is limited and there appears to be little evidence on the question of tolerance in this age group. There are, however, reports on its use with good effect (Nadas *et al.*, 1952; Moss and Thompson, 1953). Gold (1950) suggests a dosage of 3 mg./lb. body weight every three hours by mouth. The successful use of a pressor amine ,'neosynephrine', has been reported in an older child (Cunningham and Schnitzker, 1950).

It should be noted that, in view of the paroxysmal nature of the condition, it is often difficult to assess the therapeutic efficiency of drugs used to terminate an attack of supraventricular tachycardia. The administration of potentially dangerous drugs to these infants must always be considered in the light of the benign course and prognosis in approximately 80%, both in our series and in Nadas's cases of comparable age.

Other Treatment. Our patients were nursed in oxygen tents during the first 48 hours, because of cyanosis and respiratory distress. Infections were treated with an antibiotic. If sedation seemed necessary to allay restlessness and irritability chloral hydrate was given.

Prophylaxis. Digitalis was used as a prophylactic measure for at least six months following the initial attack in five cases and there were minor recurrences in three. Three patients, followed up during a similar period, to whom no digitalis was given, all had minor relapses during the first six months but not subsequently. We do not feel able to assess accurately the efficacy of this measure in view of the natural history of the condition, but short-time prophylaxis is probably worthwhile.

Discussion

Paroxysmal supraventricular tachycardia occurring in infants under the age of 6 months gives rise to a recognizable clinical picture.

Aetiology. In our series, as in that reported by Nadas *et al.* (1952), there was a high proportion of idiopathic cases; we were unable even to suggest a tentative cause for the attacks in nine of 13 infants. Two of our cases were associated with lung infection. Another was an example of acute interstitial myocarditis, an unusual condition in infancy, and corresponding to those cases described originally by Fiedler (1900). Accounts of primary or isolated myocarditis in infants have been given by House (1948), Raeburn (1948) and Lind and Hultquist (1949). Paroxysmal tachycardia is known to occur in this group in addition to other arrhythmias (Wood, 1950), and in our case the necropsy finding of a large haemorrhage in the vicinity of the sino-auricular node was of interest, but we believe it was probably agonal. Kugel and Stoloff (1933) considered that so-called congenital cardiac hyper-

trophy might be an end-result of acute interstitial myocarditis in infancy, and it is possible that infants suffering from the idiopathic type of paroxysmal supraventricular tachycardia may include examples of this form of myocarditis. We were, however, unable to find evidence of cardiomegaly on following up our idiopathic cases. The remaining case was due to endomyocardial fibro-elastosis, a condition not suspected as the cause of paroxysmal tachycardia during the few hours that the child survived in hospital. The necropsy findings were, however, characteristic. Bonham Carter (1954) has stated that this form of arrhythmia may occur in endomyocardial fibro-elastosis, but we have found no further case in any other series.

Other reported causes of paroxysmal supraventricular tachycardia in infancy have included congenital heart disease, and there were also two cases due to sino-auricular node tumours in the Boston series.

Nadas observed that the condition was far commoner in males, and of his 18 idiopathic cases under the age of 4 months only one, a day-old baby, was female. This male preponderance was not so outstanding in our series; three of nine infants in the idiopathic group were female, and of these two were aged 10 and 11 days respectively. Among 11 reported cases of paroxysmal tachycardia diagnosed antenatally, five were female (Anderson and Adams, 1953); it is possible that in some infants with paroxysmal tachycardia the disorder is perpetuated from ante-natal life, and a higher incidence of girls might then be expected in any series of very young infants.

The onset of the attack took place under the age of 1 month in 58% of the idiopathic group, i.e., five of nine infants in our series, and 14 of 24 in Nadas's series.

Clinical Diagnosis. A pattern of physical signs was found fairly consistently. Commonly an infant was noted to have attacks of cyanosis or pallor, or a combination of both, associated with collapse and cold extremities. In the very young infant these findings were often erroneously considered to be due to atelectasis or acute respiratory infection, especially when tachypnoea was observed. They are, however, compatible with peripheral vasoconstriction as a compensatory feature of a low cardiac output.

Tachycardia can easily be overlooked unless the heart rate is assessed by auscultatory methods. If tachycardia is found it is, we consider, helpful to take an electrocardiogram to record the heart rate, a procedure which should give rise to no practical difficulty even in the youngest infant.

A physical sign of considerable significance is hepatomegaly, which was present in 11 of our 13 cases. In infants the liver may increase in size rapidly while tachycardia is present, and subside in a remarkably rapid manner when normal rhythm is restored. Other signs of congestion such as a raised jugular venous pressure, basal pulmonary crepitations and oedema are not usually observed or marked in infancy. Syncope, which has been said to be common and related to changes of rhythm with transient ventricular asystole, was not noted in our series.

Electrocardiographic Findings. In all our cases the main disturbance seen in the electrocardiogram was a paroxysmal increase in the rate of auricular discharge, whether designated supraventricular tachycardia, nodal tachycardia or auricular flutter. The work of Evans (1944) and of Prinzmetal, Corday, Brill, Oblath and Kruger (1952) have demonstrated the unity of the underlying disturbances which produce the abnormal electrocardiographic records on which these diagnoses are based, and the generic term 'auricular tachycardia' is preferred to cover all disturbances now known as flutter or tachycardia. We have, however, used the older nomenclature, first, because of a possible clinical differentiation, and, secondly, because it is better known. In our series so-called auricular flutter was rare and only one certain example was found (Case 13). In another infant (Case 11) the standard leads were suggestive of auricular flutter, but no right-sided chest leads were available and it is in these leads that the diagnosis can most readily be made (Evans, 1944). It is fortunate that the differentiation of auricular flutter from supraventricular tachycardia is mainly of academic interest in infants, since the treatment of choice for both forms of arrhythmia is digitalis (Prinzmetal *et al.*, 1952).

Prognosis. Of our 10 surviving infants one has continued under observation only for six months. The remainder have been seen at regular intervals over periods varying from one to six years. After six months had elapsed following the original attack it was quite exceptional for further episodes of tachycardia to occur. This did not, however, apply to the child (Case 10) with the Woolf-Parkinson-White syndrome, although her attacks are gradually becoming less frequent. The prognosis therefore improves with age; the danger in early infancy is acute heart failure which may rapidly prove lethal. It is, however, usually amenable to treatment, especially if the condition is recognized early, as it should be at least in maternity units.

It is possible that some infants who develop paroxysmal tachycardia do not seem ill and the condition is not diagnosed. If this is so the clinical descriptions and prognosis of reported cases deal with a selected group.

Summary

Thirteen cases of paroxysmal tachycardia in infants are reported. All were supra-ventricular. The characteristic clinical and E.C.G. picture in this age group is described. Nine of our cases were 'idiopathic'; in two there was an associated pulmonary infection, in one there was interstitial myocarditis and in one there was endomyo-cardial fibro-elastosis.

Three patients died, and the necropsy findings are described.

Treatment is mainly that of heart failure, and digitalis was the most useful drug. The prognosis improves with age.

We are indebted to Dr. N. J. Brown, Dr. H. J. Heathcote and Dr. A. J. M. Reese for the necropsy reports, and to Professor C. Bruce Perry for his valuable criticism and advice.

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THE WEIGHT IN PINK DISEASE

BY

T. COLVER

From the Sheffield Children's Hospital

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It is the object of this report to draw attention to the characteristic weight trends in pink disease. The characteristic trends are not described in writings on the subject, and they merit attention since weight is the only serial observation available which is strictly objective, easily measured and uninfluenced, as are blood pressure and pulse rate, by the unfamiliar surroundings of an out-patient clinic.

Clinical Material

The hundred patients under review attended a special weekly clinic, and the series was consecutive except for six babies who recovered within five weeks of the first hospital visit and two who attended very irregularly. Of 100 patients, 47 were male and 53 female, and the average age of onset was 7½ months. Two died, in the fourth and twelfth weeks of the disease respectively, and the average duration of the disease in the remainder was 17 weeks. Appointments at the clinic were occasionally not kept, but it was usually possible to rearrange a missed appointment within two or three days. Of the 903 appointments made, 22 were missed altogether.

Management

Management followed commonly accepted principles. In an attempt to avoid unnecessary loss of weight parents were asked to quench the infants' thirst with cold milk rather than watery drinks. Chloral, phenobarbitone, sulphonamides and antibiotics were commonly used, but instructions were given that other medicaments, particularly those containing mercury, should be avoided. At the clinic each week the baby was first weighed in its clothes, the latter being weighed separately, and each weighing was checked by physician and nurse.

Serial Weight Records

The percentage weight losses during observation are shown in Table 1. Eleven babies lost 11% or more of their body weight during observation, and the records of this minority will be examined in detail since they relate only to severe examples of the disease observed in the active as well as the later phases. These detailed records are, therefore, shown in Table 2, and in the diagram the curves for 10 of the patients are plotted. Three features common to each patient will be noted: (*a*) an appreciable interval elapses between the onset of symptoms and the first hospital visit; (*b*) practically the whole observed weight loss occurs in one almost uninterrupted downward trend; and (*c*) this downward trend occurs in the early part of the observation period. For precision and to simplify comparison, these weight curves may be divided into initial, transitional and terminal stages. The transitional stage begins when the initial downward trend levels out and is defined as the first consecutive two-week period (indicated in Table 2 and in the diagram) in which there is no further overall loss of weight. The curves before and after this stage comprise the initial and terminal stages. It is now seen that the weight at the bottom of the initial downward trend is to within an ounce or so, the lowest encountered observation, the curve after this point being mainly level or rising and certainly showing no further fall in any way comparable with the initial one (except in Baby 10 who had pneumonia resistant to antibiotics in the nineteenth week). The initial stages

TABLE 1
PERCENTAGE WEIGHT LOSS DURING OBSERVATION IN 98 PATIENTS

Percentage Weight Loss	Number of Patients
0– 0·9	29
1– 1·9	6
2– 2·9	15
3– 3·9	9
4– 4·9	5
5– 5·9	6
6– 6·9	4
7– 7·9	4
8– 8·9	4
9– 9·9	1
10–10·9	4
11–11·9	4
12–12·9	2
13–13·9	3
14–14·9	—
15–15·9	2

TABLE 2

SERIAL WEIGHT RECORDS (lb. oz.) OF 11 BABIES LOSING 11% OR MORE OF BODY WEIGHT

Duration of Disease	1	2	3	4	5	6	7	8	9	10	11
1st week	—	—	—	—	—	—	—	—	—	—	—
2nd ,,	—	20– 5	—	—	—	—	—	—	—	—	—
3rd ,,	—	20– 0	—	22– 3	16–14	—	—	—	—	—	—
4th ,,	18– 6	19– 8	—	21– 9	15– 9	—	—	—	—	—	26– 4
5th ,,	17–14	18–15	—	21– 3	15– 5	—	—	—	—	—	25– 6
6th ,,	17– 3	18–11	22– 4	20–12	14–13	17–13	22–11	—	—	—	24–12
7th ,,	17– 0	18– 5	21– 8	20–10	14– 5	17– 8	21–13	—	—	—	24–11
8th ,,	16–12 *	18– 3	21– 2	20–10	14–12	16–13	21– 8	21– 1	16–10	—	23–13
9th ,,	16–15	18– 1	20– 8	20– 5	14–13	16– 6	20–10	20– 5	16– 6	15–18	23–11
10th ,,	17– 0	18– 2	19–15	19–14	14–14	16– 5	20–11	20– 0	16– 5	18– 8	23– 3
11th ,,	17– 7	18– 1	20– 7	20– 5	14– 6	16–13	20–13	19– 9	15–12	17–13	22–10
12th ,,	17–15	18– 0	19–13	20–11	15– 6	17– 3	20–12	19–11	15–15	17– 4	22– 6
13th ,,	18– 8	18– 8	19– 6	21– 3	16– 3	17– 8	20–11	19– 9	15– 2	17– 9	22– 1
14th ,,	19– 1	18–12	19–10	21– 9	17– 1	18– 0	21– 9	19–15	14–14	17–12	22– 3
15th ,,	19–12	18– 9	19–13	21–15	18– 0	18– 8	22– 3	19– 6	15– 3	17– 8	22– 3
16th ,,		18–11	20– 4	22–17			22– 7	20– 3	15– 5	17–13	22– 4
17th ,,		19– 3	20– 3	22–10		19– 3	22–11	20– 8	15– 4	17–12	22– 4
18th ,,		19– 3	20– 2			19–13	22–11	20–13		18– 1	22– 6
19th ,,		19– 9	20– 5			19–13		20–11	15– 6	18– 0	22– 9
20th ,,			20– 3			19–11		20– 9	15– 3	16–13	22–11
21st ,,			20– 6					21– 6	15– 6	17– 3	
22nd ,,			20– 6					21–11	15– 3	17–14	
23rd ,,			20– 3					22– 9	15–15	17–15	
24th ,,			21– 1						15–13	18– 5	
25th ,,									15– 7	19– 5	
26th ,,			21– 4						15– 9	19–10	
27th ,,			21– 1							19–15	
28th ,,			21–12							19–14	
29th ,,			22– 7							19–13	
30th ,,			22–13							19–11	
31st ,,			23– 4							20– 3	
32nd ,,			23– 4								
33rd ,,			23– 7								
34th ,,			24– 5								
35th ,,			24– 1								
36th ,,			24– 8								

* Transitional stage indicated in each case.

of the Table 2 group lasted on average until the tenth week of the disease (average weekly change = 7·5 oz. fall) and the average duration of the terminal stages was 10 weeks (average weekly change = 4·7 oz. rise). The form of the curves before the first hospital visits was not, of course, known, but the downward trend presumably began early, and this presumption was repeatedly confirmed by records generously supplied by Dr. K. Black, of the Maternity and Child Welfare Department of Sheffield (by courtesy of Dr. L. Roberts, Medical Officer of Health). In one patient (not of the Table 2 group) the curve was unusual in that the downward trend was delayed until the third week of hospital observation.

In short, the weight curve in pink disease consists of an early progressive trend downwards, which, once completed according to the above definition, does not show recurrences.

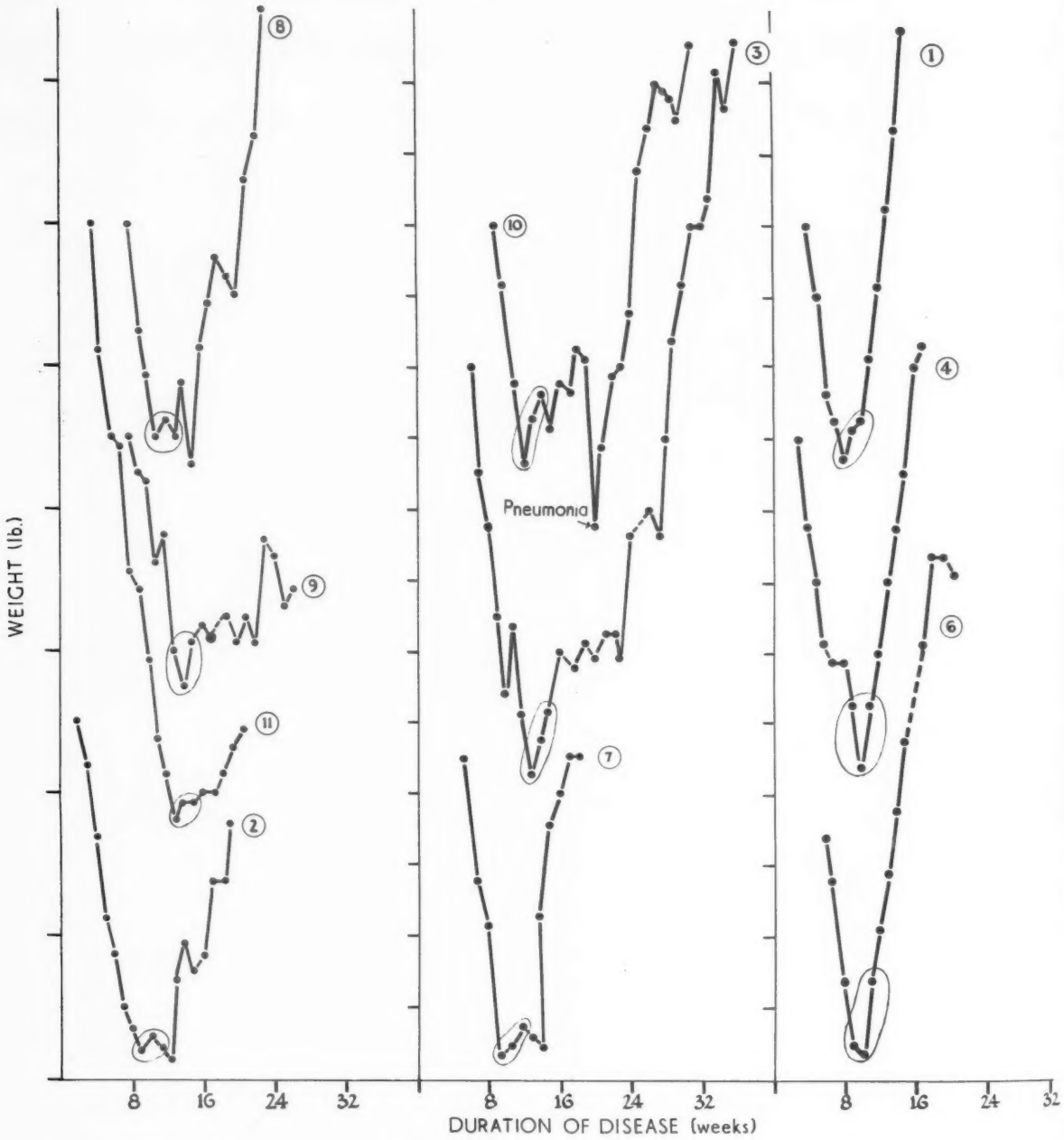
Comment

The weight curves in the diagram contrast with those commonly seen in out-patient practice since the initial down trends are not usually so marked. Thirteen per cent. of the present entire series did, in fact, show no weight loss at all during observation, but in these patients it is believed that the initial trend downwards had already occurred before the first hospital visit. There is usually considerable delay before the infants come under observation (Table 3), and it is readily understood that much or all of the initial down trend may take place during this interval, particularly if it is long or the period of fall in weight short.

TABLE 3

DURATION OF PINK DISEASE BEFORE FIRST HOSPITAL VISIT IN 100 PATIENTS

Weeks	Number of Patients
1	2
2	8
3	15
4	16
5	13
6	15
7	8
8	8
9	3
10	0
11	7
12	3
13	0
14	0
15	0
16	1
17	1



The weight curves for 10 of the 11 patients who, during observation, lost 11% or more of their body weight. The intermediate stage is indicated on each curve.

Correlation of Weight Curve with General Condition

The weight curves presumably reflect the underlying general clinical condition, but since the value of recording weight hinges on this presumption, corroboration is required. This is available to the extent that each week before the weighing records were separately kept of (*a*) the general appearances of the patient, (*b*) the gist of the mother's weekly progress reports and (*c*) the variation of individual features such as photophobia. The records cannot be shown for all cases, but a typical series is shown in Table 4.

Of the two sets of records, the mother's progress

reports are the more valuable. She alone knows the prevailing temperament and capacity to eat, sleep and take interest. The clinician's gradings, moreover, were unavoidably very coarse, but both sets of records point to complete refractoriness of general symptoms during the stage of falling weight and to the absence of relapse thereafter. The mothers' reports particularly emphasize the abruptness of the transition (the 'turn' in the parlance of many Sheffield mothers) from the initial refractory to the recovery phases. For week after week at first, the mother reports, 'He is no better'. Then there comes the week when the clinician can predict from her more cheerful expression, though not necessarily from the baby's appearance, that the 'turn' has come.

Individual Symptoms. In judging general progress the fluctuations of the more specific individual features such as photophobia were often misleading. These special features did, however, follow a particular pattern of their own which in its turn showed some correlation with the clinical stages described. At the onset of the disease it is known, for instance, that the diagnosis may not be clear, particularly if the characteristic photophobia and rash are absent and if the general symptoms are mild. The typical extremity changes, emaciation and profound hypotonia, do not, moreover, ordinarily develop for a few weeks. During the first stage diagnosis becomes easier since all features initially present become more marked and others, such as the typical changes of the extremities, make their appearance, the clinical picture gradually reaching its most florid state just before the 'turn'. Particularly at the end of this first stage the picture is dominated by general misery and debility, profound emaciation, hypotonia and extremity changes, together with photophobia and rash in classical cases. At the 'turn' there is an abrupt dissociation of clinical features, and the mother is aware of a sudden substantial improvement in temperament, even though the physical appearance of the infant remains much the same. During the recovery stage all features may henceforth improve *pari passu*, but sometimes, particularly in long-term cases, the dissociation described becomes more extreme, the general symptoms of irritability and misery clearing much faster than, for instance, the hypotonia. This gives rise to a clinical picture not unlike amyotonia congenita (Leys, 1950).

Implications

Therapeutic Trials. The existence of the two-stage course, with its progressive recovery phase, emphasizes the need for proper control during therapeutic trials and throws open to criticism most, if not all, of the trials hitherto reported in this condition. In the total series of 100 patients, for instance, the average interval between the onset of the disease and the first hospital visit was nearly six weeks (Table 1). The average interval between the onset and the beginning of the recovery phase for the 98 remaining patients was seven weeks. Improvement is to be expected, therefore, in the average hospital patient, one week after the first hospital visit regardless of the form of treatment.

Prognosis. The strain and worry imposed on the mothers of these patients is familiar and the physician gives what reassurance he legitimately can. The greater predictability afforded by a knowledge of the foregoing trends helps him in this respect. In general, instead of just being able to tell the mother that the average duration for hospital patients is approximately four months (this was the figure in this series; see also Fisher, 1947) he can add that the worst of the disease is likely to be over in two months. He can also predict a progressive recovery phase as soon as there comes a period of two consecutive weeks with no overall weight loss.

TABLE 4

TYPICAL CORRELATION BETWEEN WEEKLY WEIGHT CHANGE, MOTHER'S PROGRESS REPORT AND THE CLINICIAN'S OBJECTIVE GRADINGS

Duration of disease in weeks ..	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Weight change in ounces				−7	−6	−7	−4	−5	+2	+5	+7	+1	+0	+5	+2	+6
Mother's progress reports*			↓	↓	0	0	0	0	↑	↑	↑	↑	↑	0	↑	Recovery
Clinician's objective† gradings ..			3	3	3	3	3	3	3	2	2	2	2	2	1	Recovery

* The symbols indicate: ↑ substantial improvement, ↓ substantial deterioration, and 0 no appreciable change, and the numbers 1, 2, 3 and 4 the clinician's assessment of general condition as judged by general appearances.

† Grade 4, severest grade, typical appearances, patient gravely ill and causing anxiety as to immediate survival, periods of prostration alternating with periods of typical irritability; Grade 3, typical appearances, inability to take interest and no smile, but no anxiety as to immediate survival; Grade 2, similar to Grade 3, except for short periods in which the baby takes a little interest in surroundings and in which it may smile for a few moments; Grade 1, mildest grade, clinician sees no satisfactory evidence of active disease, but the mother reports that the baby is not by any means recovered.

Aetiology. The possible role of mercury as a cause of this disease is today constantly under discussion and any fresh impressions as to the natural course of the disease must be considered in this connexion. So far as they go the findings of this report support the mercury hypothesis: i.e., (*a*) the older editions of the standard textbooks (Sheldon, 1946) emphasized the unpredictable ups and downs of the disease; (*b*) this was the course to be expected if mercury were responsible and no steps were taken to withhold its further administration during treatment; (*c*) in the series under review instructions were given that no further mercury should be taken during treatment and unpredictable ups and downs have been absent. The course has presented, on the contrary, just the pattern to be expected if mercury is responsible, i.e., an initial refractory phase until the bulk of the mercury has been excreted and thenceforth the progressive recovery phase to be expected once the metal has been removed.

Summary

The weight curve in pink disease may conveniently be considered in two distinct stages.

The initial stage consists of a progressive downward trend commonly lasting for eight weeks.

The terminal stage consists of a level or rising curve which is, barring intercurrent infection, free from any appreciable weight falls.

From the general clinical viewpoint, the main finding was the good correlation between weight and general condition with the conclusion that pink disease in all its aspects follows a two-stage course: an initial stage with active refractory symptoms and progressively falling weight, and one of recovery with gradual general improvement, a level or rising weight and no relapse.

I should like to thank Mr. A. S. Foster, medical artist to the United Sheffield Hospitals, for the diagram, and Dr. T. Lodge and Dr. J. C. Haworth for their criticism.

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SUDDEN MENTAL DETERIORATION WITH CONVULSIONS IN INFANCY

BY

R. S. ILLINGWORTH

From the Children's Hospital, Sheffield

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A wide variety of diseases in infancy is associated with convulsions and mental deterioration. In many there are spasticity, ataxia or other abnormal neurological signs. In other children presenting with convulsions followed by mental deterioration there are no abnormal neurological signs apart from those of the mental changes.

Most writers ascribe the mental changes to the convulsions, though a few have suggested that both fits and mental deterioration may be due to underlying disease of the brain. From experience at the Children's Hospital, Sheffield, I believe that there is a clear-cut group of cases in which a child develops normally up to a certain age, and then practically simultaneously develops fits and mental deterioration. I have not found a reference in the literature to this type of case. In a second group development proceeds normally up to a certain age, and then fits develop; at some subsequent period, often many months or years later, mental deterioration becomes manifest. This paper describes cases belonging to the former group.

The Present Study

Between 1947 and 1954 I have seen 12 children who developed normally for a period and then almost simultaneously developed epilepsy and underwent mental deterioration. None of the children were born prematurely. Only one of the 12 children (No. 10) had an abnormal delivery, and he was the only one who was ill at birth or in the immediate post-natal period. In none of the other children was there any history of asphyxia at birth, vomiting, cyanotic attacks, respiratory or feeding difficulties, convulsions, twitching or cerebral irritability. In only one child (No. 9) was there a family history of epilepsy; in this case a sibling, who was doing very well at an ordinary school, had petit mal attacks. A cousin of one boy (No. 7) was mentally defective, but there was no other history of mental defectiveness in the family.

All 12 children developed normally for the first few weeks of life, responding at the usual age to social overture, vocalizing, taking interest in their surroundings and using their hands in the normal way. All were well, thriving children, with a good weight and no evidence of rickets.

The age of onset of the illness in these children was 4 to 8 months. In five cases the onset was at 5 months of age. There was no precipitating factor for the illness in any case. No child had any injury, fever or diarrhoea before the onset of the convulsions or mental change. One child (No. 6) had a trivial cold, without fever, at the time of the onset of the fits.

In eight children fits were the first abnormality noted. In the remaining four there were probable premonitory symptoms. One child (No. 1) cried excessively for the two weeks before the first convulsion, having previously been well behaved. Another (No. 3) was said to 'look vacant' (all through the day) for a week before the convulsions occurred. Another (No. 4) became irritable six weeks before fits were noted, taking much less notice of his surroundings and crying continuously, even in his mother's arms. The other child (No. 10) stopped smiling and became dull and staring two weeks before the first fit. In six children the first fits noticed were minor motor convulsions, using the classification adopted by Livingston (1954). In a further five children the convulsions were of the major motor type, and in one they were 'salaam spasms' or akinetic seizures.

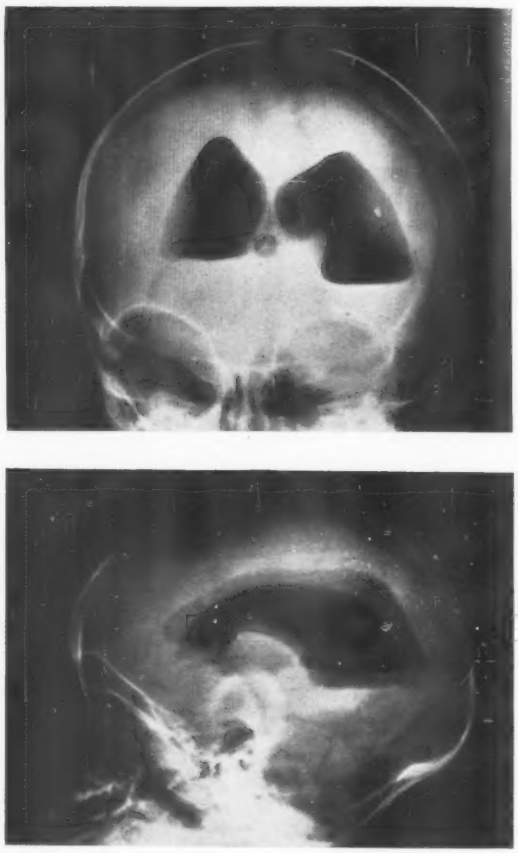
The striking feature in the history of all cases was the sudden change in the social responsiveness and in the interest in their surroundings. All eight children whose first symptom was a fit, from the time of the first convulsion, or at least within a day or two of it, stopped smiling and laughing and stopped taking an interest in their surroundings, becoming dull and apathetic. It was only after several months that these children began to smile again, and to show interest in the environment, and

then the smiling was only occasional, at least for many months, and the interest shown in the surroundings was only fleeting.

The children were first seen by me at varying intervals after the onset. In eight children who were seen within eight weeks of the onset, there was a remarkable dissociation or lack of parallelism between the relatively normal or quite normal motor and manipulative development and the absence of smiling and laughing, and the total lack of interest in the surroundings, so marked in three cases that it was thought (wrongly) that the children were blind. Though this was only to be expected, in view of the previous normal development, the finding is most unusual, and the unwary, assessing a child merely by the development of sitting and locomotion, would fail to notice the highly significant 'intellectual' changes. In two of these children, seen very shortly after the onset, I gave the parents a bad prognosis on the grounds of these 'intellectual' changes, in spite of normal motor development, and the prognosis proved in later years to be correct, for they are now both aments. In none of the children seen early after the onset was there any significant retardation in motor development and in the use of the hands.

In all cases the rest of the clinical examination was negative, there being no other abnormal neurological signs or abnormal signs elsewhere. The fundi in all cases were normal. The head size, the anterior fontanelle and the cranial sutures were normal.

All investigations with the exception of air encephalograms and electroencephalograms were negative. The Wassermann reaction was negative in all 12 children. The urine of none of the 12 children contained phenylpyruvic acid. A radiograph of the skull was taken in 11 of the children and was normal in all. Tests for toxoplasmosis were carried out in five and were negative. The cerebrospinal fluid was examined in six children within a month of the onset and in two other children at a somewhat later date, and it was normal. In retrospect it is regrettable that subdural taps were carried out only in four children. All were negative. The serum calcium was estimated in two children. It is also regrettable that air encephalograms were only carried out in two cases (Nos. 6 and 9). Livingston (1954) described a child who had a known cerebral haemorrhage at birth and who developed normally until the age of 5 months, when a fit occurred. An air encephalogram showed a cyst in the right frontal region which was removed: the child subsequently improved, though with a residual low I.Q. (69). In Case 6 the air encephalogram at the age of 3 years and 8 months was normal. In Case 9 there was distension of the ventricles, but no definite evidence of cortical atrophy (Figs. 1 and 2).



FIGS. 1 and 2.—Air encephalograms of Case 9 at the age of 7 months, showing a considerable degree of symmetrical hydrocephalus. The subarachnoid spaces are not filled with air and cortical atrophy is not demonstrable.

Electroencephalography, using the standard bipolar technique, were carried out at various times in 11 children by Dr. Warboys.

In four cases a tracing was obtained within three months of the onset of the fits and three of them are illustrated here (Figs. 4, 5 and 7). The records of these early cases are all grossly abnormal and contain much generalized paroxysmal slow activity with spikes. The latter vary in location, sometimes appearing focal but actually involving all areas over a period of time. The spikes bear no constant relationship to the slow waves, as they do in petit mal, or to slow spike-and-wave discharges, and these records are quite different from those in petit mal or its variants.

Focal abnormality was found only in Case 1

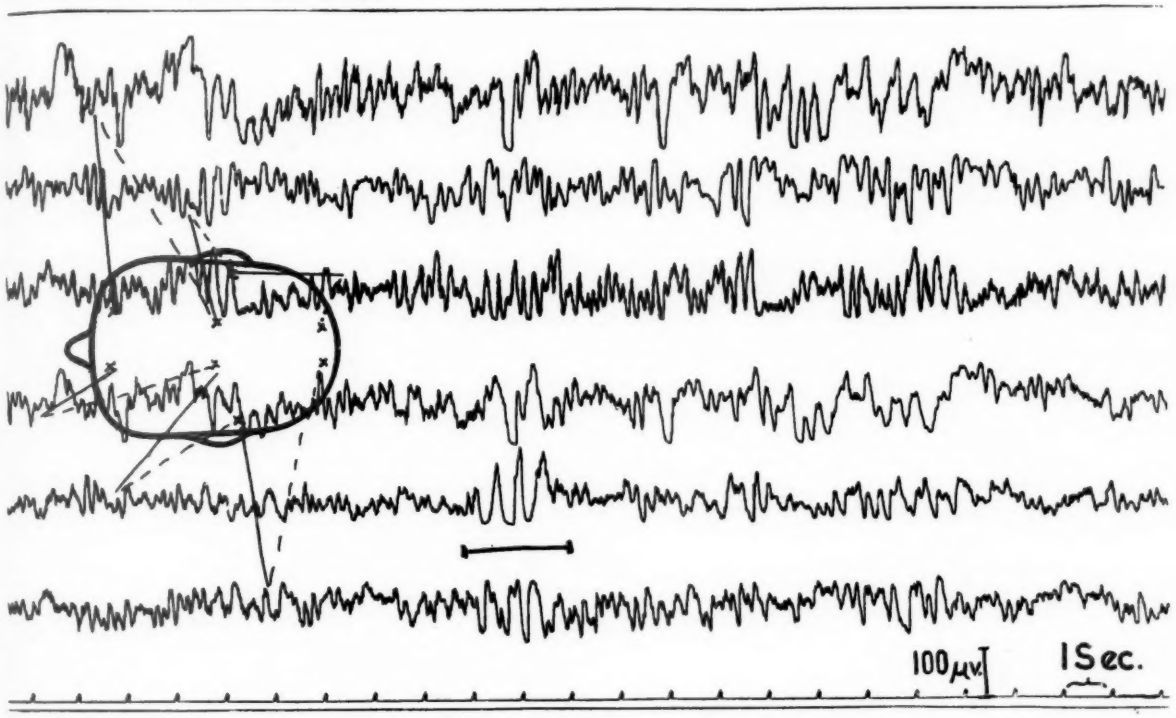


FIG. 3.—Case No. 1, aged 3 years and 3 months, the only case in the series with a focal abnormality—a left temporal epileptogenic focus. Awake—off drugs.

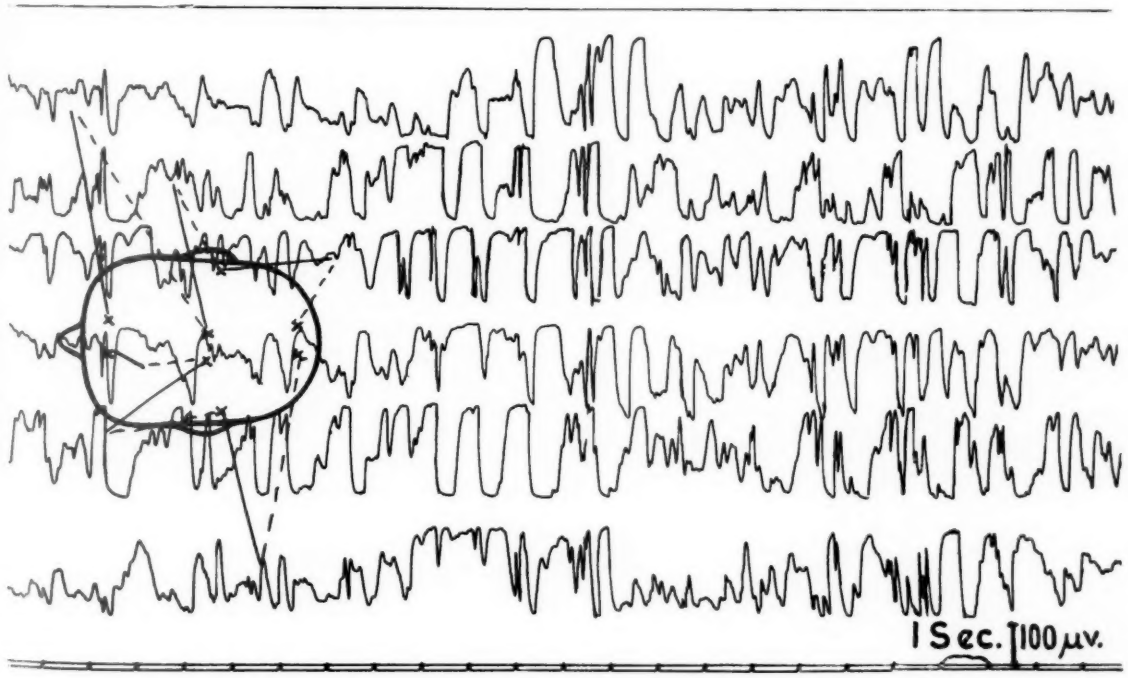


FIG. 4.—Case No. 2, aged 7 months. Light natural sleep, off drugs. Generalized spikes with irregular high-amplitude slow waves.

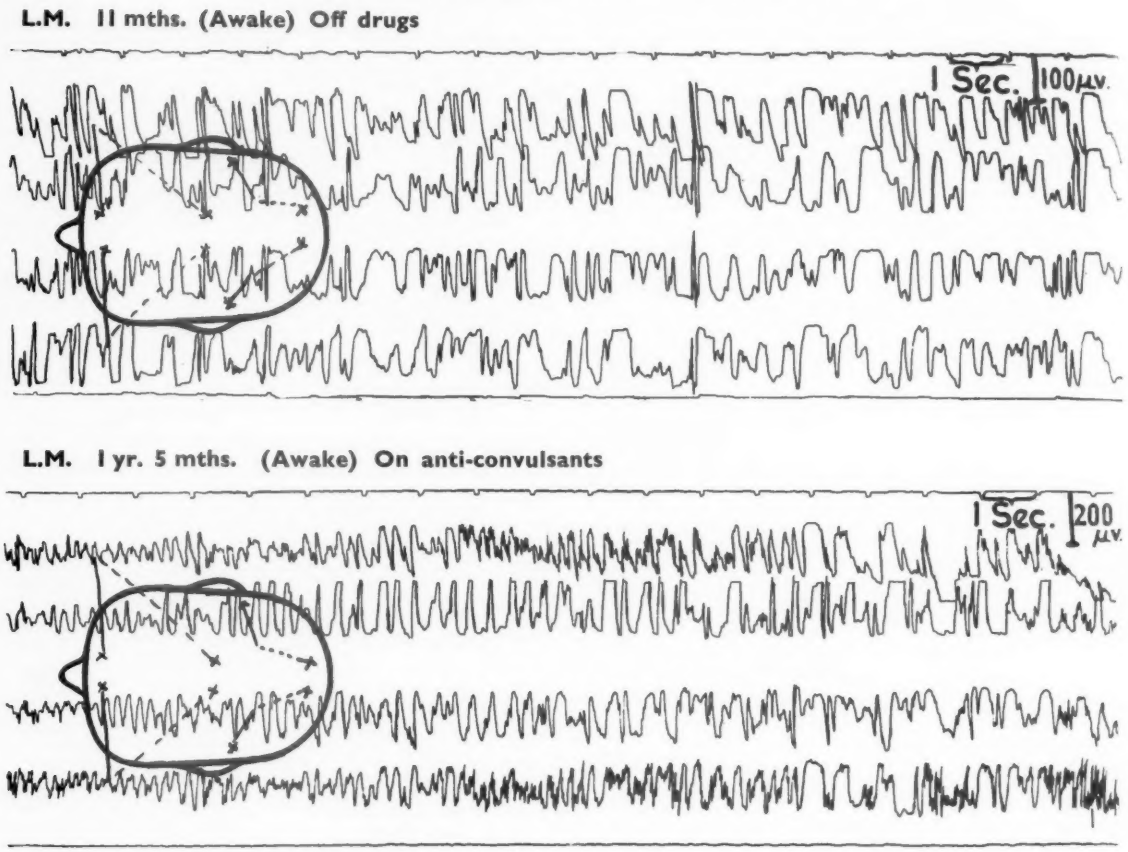


FIG. 5.—Case No. 5, aged 11 months. Awake, off drugs. Generalized spikes and high-amplitude paroxysmal slow waves, with only slight improvement at 17 months on anticonvulsants.

(Fig. 3) and consisted of a paroxysmal slow wave focus in the left temporal lobe. Unfortunately, the first tracing was taken some three years after the onset of fits.

In every case an improvement in the degree of dysrhythmia was noted with age. Little change could be detected within the first two or three years (Fig. 5) in spite of anticonvulsant therapy, but by the age of 4 to 5 years a marked improvement in the tracing was universal (Fig. 6). Seven of the patients are now aged 4½ years or more and recent tracings were obtained in six of them. The abnormality in these later records consisted of only a mild dysrhythmia with rather a wide range of frequencies for their age and occasional short bursts of generalized slow waves.

The E.E.G. findings indicate a defect of the brain, resulting in a period, between the ages of 5 months and 5 years, of high amplitude explosive electrical activity with fits and amentia.

Clinical Course

In spite of treatment, consisting of phenobarbitone, phenytoin, troxidone, primidone or metharbital, the fits were for the most part incompletely controlled, though there was a tendency for the fits to cease with age. All the children had several fits a day for several months. It is notable that eight of the children developed akinetic seizures or salaam convulsions, and one had these at the onset, making a total of nine. In all these nine the salaam attacks were very frequent, up to 40 a day being noted by the parents. It is well known that these attacks respond badly to treatment, but in retrospect it is clear that the drugs used were not pushed to the limit of tolerance and that insufficiently determined efforts were made to control them. Nevertheless, from the experience of others it is doubtful whether we could have achieved significantly better results.

As for the general development of these children,

Case 2 has not been followed up sufficiently long for final assessment. Some of the parents thought that after a few months the children improved, but it was clear on examination that their mental age was not gaining or even keeping up with their chronological age. Case 4, 46 months after the onset, had progressed surprisingly well, and his I.Q. was in the region of 60. All the others, without exception, were aments, with an I.Q. too low to assess.

Below are brief summaries of the case histories of these children.

Case Histories

Case 1. This girl began to smile at 6 weeks of age and to laugh aloud at 4 months. She turned her head to sound at 3 months. She was able to take hold of objects at 5 months.

At 5½ months she began to cry a great deal without apparent reason, but appeared to be normal otherwise until fits began two weeks later. In the fits the limbs seemed to tremble, there was conjugate deviation of the eyes upwards, and the arms stiffened. Each attack lasted for a few seconds, and there were three or four a day from that time onwards. From the time of the first fit, smiling ceased, and the baby stopped taking an interest in her surroundings. She lost her ability to grasp objects.

On examination at 9 months her motor development was that of a 6-month-old child, and she was unable to grasp objects. There was a notable lack of interest in test objects and an absence of smiling and play. Sub-

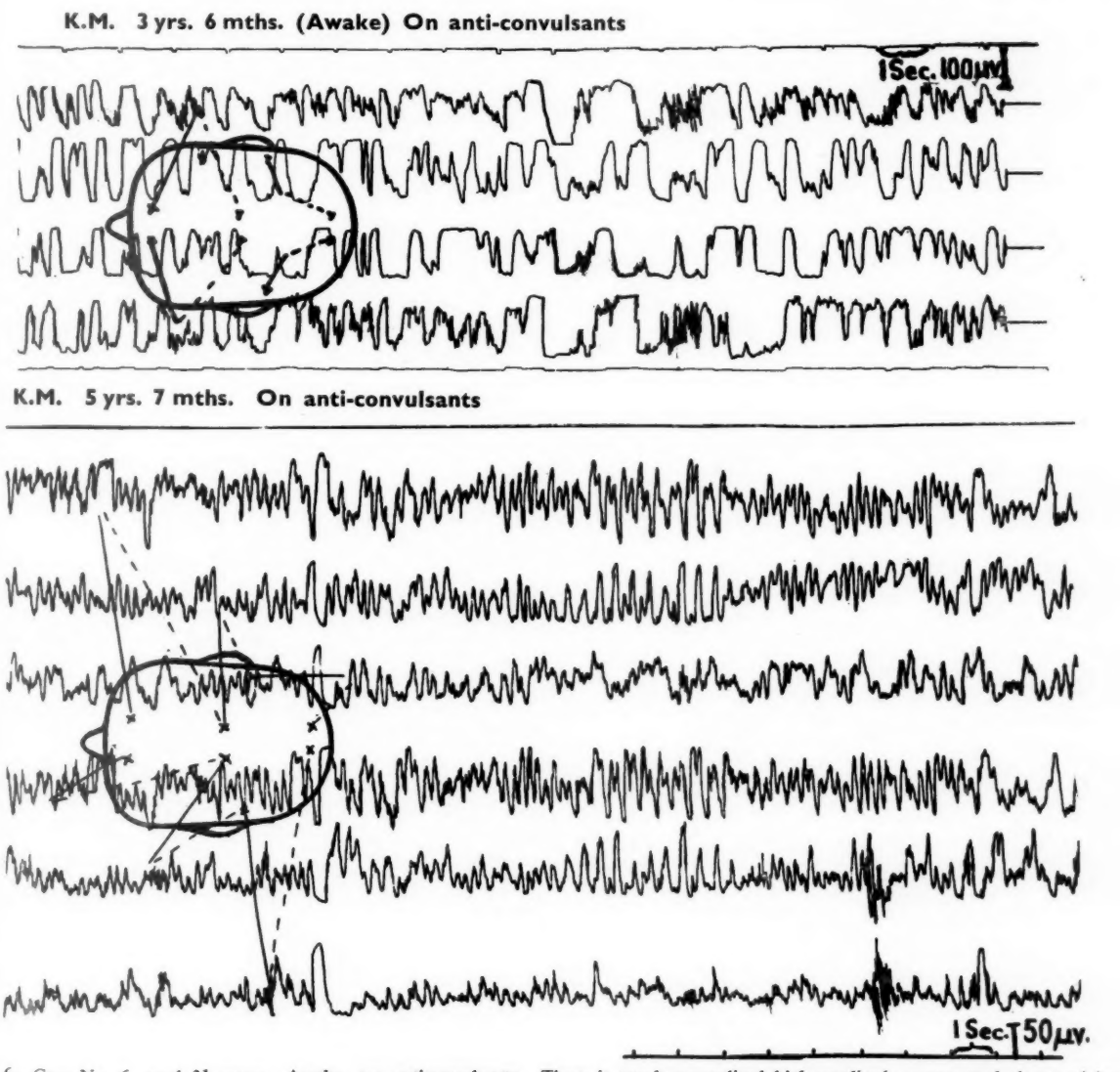


FIG. 6.—Case No. 6, aged 3½ years. Awake, on anticonvulsants. There is much generalized high-amplitude paroxysmal slow activity which has almost entirely disappeared by the age of 5 years and 7 months.

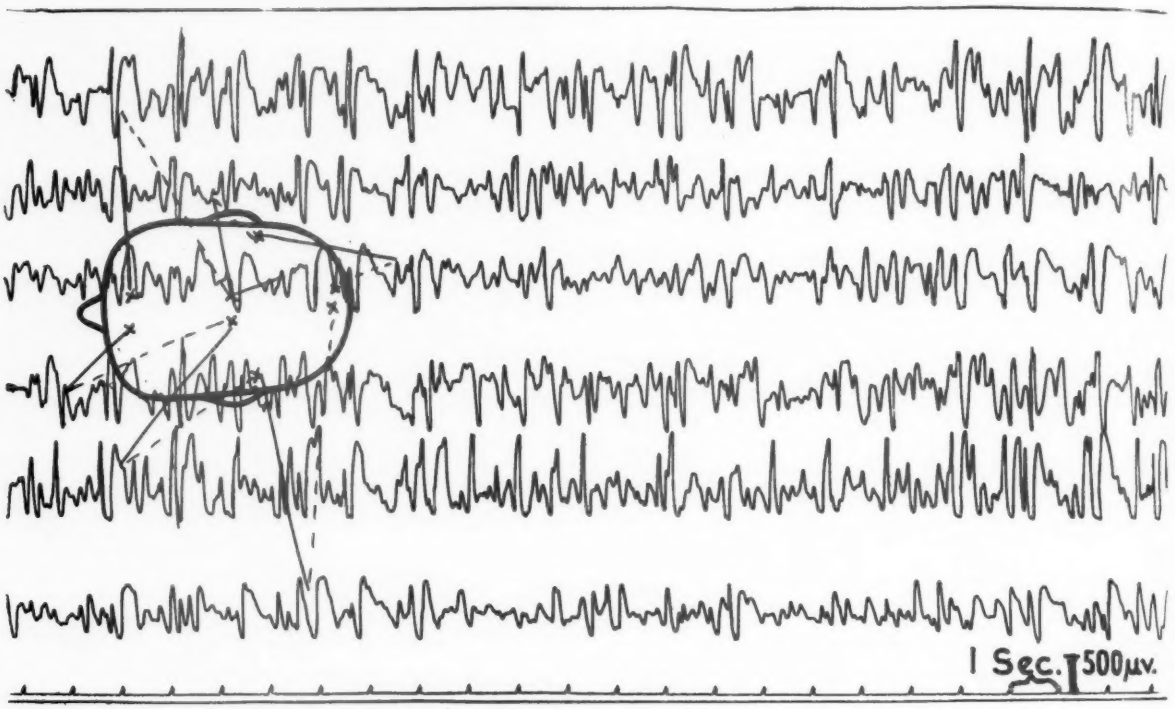


FIG. 7.—Case No. 9, aged 6 months. Waking record, off drugs. Extremely high voltage record with generalized spikey waves.

sequent examination at intervals confirmed the impression of severe mental deterioration. At the age of 3 years and 3 months she was a hyperkinetic destructive idiot. There had been no fits for six months.

Case 2. This boy began to smile at social overture at 6 weeks, and smiled at 3 months when his mother came into the room. He would hold objects for prolonged periods when they were placed into his hands at 4 months, and could reach out and grasp objects at 5½ months. He transferred objects from hand to hand at 6 months. He rolled from supine to prone at 4 months, could sit propped up for half an hour at 4½ months, and unsupported at 6 months.

At the age of 7 months he had a convulsion, lasting one or two minutes, consisting of dropping of the head, conjugate deviation of the eyes upwards, and of twitching of the left arm, followed by sleep. After that time, for the next three months, he had about seven attacks a day, in spite of treatment with phenobarbitone and phenytoin. He developed salaam spasms at the age of 8 months.

He stopped smiling within a day of the first convulsion, whereas previously he had been a happy baby. He used to laugh aloud repeatedly: with the onset of the fits the laughter stopped.

On examination (at the age of 9 months) there was a striking dissociation between the normal motor development and the absence of interest in his surroundings and in the test objects, and in the absence of smiling, laughing and play. Subsequent examination confirmed the diagnosis of mental deterioration.

Case 3. This boy began to smile in response to overtures at 6 weeks, and to vocalize when talked to at 8 weeks. At 3 months he would hold a rattle placed in the hand and play with it for some minutes. At 4 months he was said to be able to raise his head from the supine position. He would hold his feeding bottle, and would laugh aloud. In all respects he was developing normally.

At 4 months of age he was noticed to have a vacant look for a large part of the day, and a week later he had a fit, in which there was conjugate deviation of the eyes upwards; he was stiff and unconscious. He had about 20 fits a day for three days. There were no more fits for three weeks, but then they recurred. From the time of the first fit smiling and vocalizing ceased, and he appeared disinterested. He would take little notice of his mother when she lifted him up in her arms. He stopped taking interest in his food, and seemed lifeless. He did not appear to notice his toys, which previously he had enjoyed.

On examination at the age of 6 months, his motor development was normal. There was no spasticity. He could roll from supine to prone and head control was full. He could sit without support for a few seconds. The fontanelle and head circumference were normal. He showed so little interest in his toys that blindness was suspected. He would not follow the dangling ring.

There was no smiling. Minor motor fits and salaams were observed.

Examination at subsequent dates confirmed the original impression that he had a degenerative condition, but vision was normal. He is now 5 years old, and is in a mental institution.

Case 4. This boy began to smile at 6 weeks and to laugh aloud at 3 months. He could raise his head from the supine position at 5 months, and drink from a cup at 6 months. He developed normally till 6 months. At 4½ months he became irritable, began to take less notice of his surroundings, and cried excessively even when picked up. At 6 months he began to have minor motor attacks, in which he became pale, stared for a second, had a sudden jerk, screamed and fell forward. He had about four a day. From that time onwards all smiling and laughing ceased.

When seen at the age of 7 months his motor development was that of a 5- to 6-month-old baby. He took little interest in his surroundings or in test objects. He would neither hold objects nor follow them with his eyes. Salaam spasms had occurred over the last month. The fits came under control, and from the age of 8 months to 3 years and 4 months he had no fits. He then had a minor motor convulsion, but there had been no further fits when he was last seen at the age of 4 years and 4 months. There had been no further deterioration, his I.Q. being assessed at 58.

Case 5. This boy began to smile in response to overtures at 4 weeks, to sit without help at 6 months and to stand, holding on to furniture, at 8 months. In all other respects he developed normally till the age of 8 months, when he had a major convulsion, lasting for one minute, followed by a two hours' sleep. There was no associated fever. After the fit he was irritable, cried a great deal, but was eating normally. He seemed a different baby, just sitting in the pram and staring. He did not seem to take any notice of his surroundings, and all smiling and laughing stopped. He no longer reached out for objects. He had a further fit three days later and yet another four days after that. He was admitted four days after the first convulsion, and there were no abnormal physical signs other than those above. The cerebrospinal fluid and a radiograph of the skull were normal. The Wassermann reaction was negative. There was no phenylketonuria.

Salaam spasms developed at the age of 10 months, and fits occurred continuously for two years, in spite of treatment with phenobarbitone, phenytoin, 'primidone' and 'metharbital'.

His progress from the age of 8 months was that of a mentally defective child. He was seen at frequent intervals. He began to creep at 16 months and to walk at 24 months. By the age of 30 months he had not begun to say any words. His parents said that they could not teach him anything. He had difficulty in chewing solid foods and could not feed himself. There was no sphincter control. He was grinding his teeth. He was a hyperkinetic idiot, and developmental tests were impossible.

Case 6. This girl began to smile at 5 weeks, and was following her mother's movements with her eyes at 8 weeks. She was able to grasp objects held in front of her at 5 months. She developed normally in all ways until 5 months, when she began to have minor motor fits. In these there was conjugate deviation of the eyes, the head was thrown back, the legs became stiff and she turned her feet in. The arms were then thrown out, and she gripped objects tightly. The attacks lasted for a few seconds only, and there were four or five a day. From the first day she was miserable, whimpered a lot and smiling ceased. The appetite remained unchanged.

She was seen three weeks after the onset, and in view of the change in the social behaviour a bad prognosis was given. There were no abnormal physical signs other than those above.

She was seen at repeated intervals. Salaam spasms began at the age of 9 months. The fits were uncontrolled by the usual treatment up to the age of 3, when they ceased. She began to sit without help at 12 months, and to walk at 17 months. At the age of 5 years she was not saying any words. There was no sphincter control. She was a grossly retarded child with an unscorable I.Q. Fits had recurred.

An air encephalogram at the age of 3½ years was normal.

Case 7. This girl began to smile and to follow her mother with her eyes at the usual time. She could reach out and grasp her rattle at 5 months and between 4 and 5 months would play for hours with the straps of her pram. She was a happy, smiling, laughing baby until at the age of 6 months she had a convulsion. In the attack she appeared to choke, to shake from head to foot, the eyes turned up, she became stiff and the legs and arms twitched. The fit lasted for three or four minutes. Smiling ceased from the time of the first fit.

On examination at 18 months she was a severely retarded girl, with practically no interest in her surroundings. Her motor development was that of a 5-month-old baby. She had several fits a day until the age of 2, but when last seen at the age of 4½, she had not had a fit for two and a half years. She could only say two words with meaning and was incontinent. Her I.Q. was too low to assess.

Case 8. This boy began to smile at 6 weeks. At 5 months he was able to reach out and grasp objects. He developed normally till the age of 6 months, when salaam spasms developed, and within a day or two all smiling ceased. He did not smile again for six months. He lost his ability to grasp objects but re-learnt the skill at the age of a year. He took no notice of anything for about six months, and just sat still in his pram, without moving the canvas covering. He had a major epileptic fit at the age of 2 years and 11 months. Salaam spasms occurred many times a day.

He was last seen at the age of 5 years and 10 months,

when he was a hopeless ament and an I.Q. test was impossible.

Case 9. This girl developed normally, smiling, taking notice, playing and responding to sound, up to the age of 5 months, when she had a series of four major convulsions on one day and was admitted to hospital. From the day of the first fit onwards she stopped smiling. On admission she took so little interest in her surroundings that she was thought to be blind. A general convulsion was seen. An air encephalogram showed some distention of the ventricles. Apart from this and the electroencephalogram other investigations were negative. Her progress ceased, and when last seen at the age of a year she was an ament, with practically no head control.

Case 10. According to his mother, this boy had a difficult forceps delivery, and was shocked and ill after birth, with some twitching. He developed normally till 4½ months, having begun to smile, vocalize, look round and take notice at the usual time. At 4½ months he stopped smiling, became dull and staring for two weeks without apparent reason, and then developed major motor convulsions, seven or eight a day, each lasting one to two minutes. He would then lie for hours, doing nothing and not moving. All investigations were negative. At the age of 16 months he was a complete ament, with frequent salaam spasms and occasional major motor attacks. At the age of 3 years and 3 months his I.Q. was too low to assess.

Case 11. This boy was smiling at the usual time and following his mother with his eyes at 3 months. At 5 months he developed minor motor convulsions, with rolling of the eyes and sudden stiffening. Salaam spasms developed at 6 months. Immediately after the first fit he stopped taking notice of his surroundings, and showed no interest for a further 10 months. The fits were uncontrolled, occurring three or four times a day, and about 40 salaam spasms occurred every day.

He learnt to sit at 10 months and to walk at 18 months, but there was a striking lack of interest in his surroundings and lack of concentration. At the age of 4 years and 8 months he was an ament, with much toothgrinding, and unable to say any words, with an I.Q. which was too low to assess. Phenobarbitone, 'troxidone,' phenytoin and 'primidone' had failed to control his fits.

Case 12. This boy developed normally up to 4 months. He had begun to smile at 4 weeks. At 4 months he had a minor motor convulsion, becoming pale, looking vacant, with jerks of the head and several episodes of stiffening. He stopped watching people and showed much less interest in his surroundings, becoming listless. One to three fits occurred every day in spite of treatment. He began to sit at 9 months and to walk at 15 months, but he was unable to say as much as three single words till he was 2 years old. There was a striking dissociation between his motor and intellectual development. Progressive deterioration occurred, and at 2 years he was wrongly thought to be blind and deaf, on account of the lack of interest in his surroundings. He had numerous salaam spasms up to the age of 2. When seen at the age of 5 years and 9 months he was an ament, with an I.Q. too low to assess. He had had only one fit in the last two and a half years.

Discussion

Though it is well known that repeated epileptic fits may be followed in time by mental deterioration, the clinical picture which I have described, namely, a period of normal development followed by the sudden and almost simultaneous onset of fits and mental deterioration, does not appear to have attracted attention. Friends in other centres have told me, however, that they not infrequently see this picture. Whether it occurs in older children is not certain. I saw a child at the age of 8½ years, one of 10 children, six of whom had died between the age of 8 months and a year with fits: she was said to have learnt to sit without support at 7 months and to walk without help at 10 months, and then to have developed fits and simultaneous mental deterioration at the age of 3 years; she was severely mentally defective when I saw her, with no other abnormal physical signs. Owing to the long interval, however, between the onset of the fits and the time I saw her and took the history, the story may have been inaccurate.

It is notable that in all the cases which I have described the mental development was normal for the first few weeks. Livingston (1954) wrote: 'We have studied a group of 570 patients in whom mental retardation and recurrent convulsive seizures appeared during the first year of life. Evidence of mental retardation was present in all of them prior to the onset of convulsions.' This series included, presumably, children with abnormal neurological signs, such as those of cerebral palsy. I have seen a child who had evidence of backwardness before fits occurred, but who then deteriorated immediately and severely. There was no family history of fits or of mental defect. He began to smile at the age of 3 months, and to vocalize and take interest in his surroundings about a month later. At the age of 4 months he developed convulsions and forthwith stopped smiling and showing interest in his environment. When seen by me at the age of 9 months he was an ament with frequent fits and grossly defective motor development, his head control being little better than that of a 6-week-old baby. This boy differs from the series of 12 cases described above, not only in the evidence of previous backwardness, but in the gross defect of motor development. In the other patients who were seen shortly after the onset, the striking feature was the normal motor

development, confirming the mother's history of previous normal progress, with grossly abnormal social behaviour.

The nature of the pathological lesion in these cases is a matter of conjecture, and it is unfortunate, as already stated, that more air studies were not performed, but at the time they did not seem to be justified. The absence of an abnormal birth history, and the fact that all the babies were full term, is striking. There are many who feel that a normal delivery, with the absence of any signs of birth injury in the immediate post-natal period, by no means excludes the possibility of such injury (Penfield and Jasper, 1954). At the Jessop Hospital for Women at Sheffield, we follow up all babies with an abnormal birth history, including all those who suffered from asphyxia, neonatal convulsions, cerebral irritability and cerebral haemorrhage, but in eight years I have never seen one develop the picture which I have described. Nevertheless, it is possible that birth injury is the cause of the syndrome, though it is difficult to understand the mechanism involved.

The clinical picture of the cases described does not in the least suggest that the fits are the cause of the mental deterioration. In this connexion the mental changes in four of the children before the fits began are of particular importance. The immediate or almost immediate onset of mental changes in the remaining children, following in six cases a minor motor seizure lasting for a few seconds only, makes such a cause of the deterioration unlikely. It is well known that the much more severe febrile convulsions do not lead to any mental deterioration. It is far more likely that some change occurs in the brain which causes both the fits and the deterioration. The absence of any preceding infection, especially diarrhoea, and the absence of any abnormal neurological signs, make thrombosis or haemorrhage improbable.

The high incidence of salaam spasms or akinetic seizures in these cases is of interest. It may well be that, as Bridge (1949) suggested, they are due to a deep and diffuse brain lesion, and that this explains the view that they are usually associated with severe mental deterioration, and that they are difficult to control.

The E.E.G. picture in our patients was identical with that described by Gibbs and Gibbs (1952) under the title 'Hypsarthymia' in a series of 132 infants with similar motor convulsions. In two-thirds of their patients there was no known aetiology, but they regarded the changes in the E.E.G. as indicating a diffuse lesion of the brain, possibly due to a bacterial or virus disease in the mother during gestation. They did not mention, however, the developmental history of the infants before the seizures began.

In assessing the prognosis in an individual infant who develops fits without abnormal neurological signs or known cause, such as fever, it must be remembered that in the vast majority of cases, provided that the fits are brought under control, no mental deterioration will ensue. The various studies which have been made of the subsequent intelligence of children who had convulsions in infancy are of little value in assessing an individual. One difficulty is that these studies bunch together convulsions of different aetiology, instead of separating them off into the various types and causes. In my opinion the prognosis can only be assessed by a thorough developmental examination, with special emphasis on the child's social behaviour, his responsiveness, alertness, and interest in his environment. If these are abnormal, the prognosis should be very guarded, until repeated observation permits a more definite statement. It must be borne in mind that excessive irritability, the loss of smiling, and a reduction in the interest in surroundings may be due to many causes, and a thorough physical examination is necessary in all cases.

Summary

Occasionally an infant develops normally for a few months and then suddenly develops fits and mental deterioration without apparent cause and without abnormal neurological signs other than those of retardation.

Twelve cases of this type are described. In four of them certain changes occurred in the child's behaviour shortly before the fits developed: in the others there was a change in the child's behaviour, notably the stopping of smiling and of interest in his surroundings, immediately after the first fit. On examination shortly after the onset there was a striking dissociation between the child's normal motor development and the defective social responses. Severe mental deficiency followed. It was thought that these cases must be due to an underlying brain lesion.

My thanks are due to Dr. J. W. Warboys for the electroencephalograms and for reporting on them, to Dr. T. Lodge for the *x*-ray studies and to the Photographic Department of the United Sheffield Hospitals for the reproductions. I also wish to thank the family doctors who referred the children to me. One of the patients is under the care of Dr. T. Colver, to whom I express my thanks for permission to record the details of this boy and for allowing me to examine him.

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A FORM OF LIPOIDOSIS OF THE ADRENAL CORTEX IN AN INFANT

BY

A. T. SANDISON

From the Departments of Pathology, Royal Hospital for Sick Children, Western Infirmary and University of Glasgow

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The lipoidoses, or diseases of lipoid metabolism, have been extensively studied in recent years. No case similar to that described below has been discovered in the literature, the essential feature being the restriction of the process to the adrenal cortices and to heterotopic adrenal cortex. The adrenals were enlarged, pale and obviously grossly abnormal, the cortex being replaced by xanthomatous cells.

The lesion, in its fully developed state at least, is not likely to be missed even on cursory examination. As no cases have been traced the condition is probably one of considerable rarity.

Case Report

The child, a female, was born at home, weighed 2·8 kg., and failed to thrive despite repeated changes in the feeding régime. She was admitted at the age of 3 months to the Royal Hospital for Sick Children, Glasgow, five days before her death when she was noted to be obviously marasmic and to have a dusky pigmentation of the skin. A systolic murmur was heard at the heart base. Her condition continued to deteriorate despite intravenous fluid therapy. No hormone assays were made.

At necropsy (P.M.8831) the body weight was 3·4 kg., the normal body weight for this age being at least 5 kg. Pigmentation was not obvious in the light of the post-mortem room. The heart showed a patent ductus arteriosus. The alimentary tract appeared normal and culture of the intestinal content for pathogenic organisms was negative. The only significant finding was that both adrenals were large, firm and pale (left adrenal 3 g., 4 × 2 × 1 cm.). At this age the normal combined weight of the adrenals is 2-3 g. On section, the glands were putty-white, with no evidence of haemorrhage (Fig. 1). The remaining endocrine organs appeared normal.

Histological examination of the heart, trachea, thyroid, thymus, major bronchi, lungs, liver, spleen, pancreas, mesenteric lymph nodes, bowel, spinal cord, medulla oblongata, cerebral cortex, breasts, uterus, tubes and ovaries showed no significant abnormality.

The adrenals showed complete absence of the normal architecture except for occasional scattered islets of recognizable medullary tissue. The cortex showed no trace of the usual zonal arrangement (Fig. 2). The cortical cells resembled neither those of the adult nor of the foetus nor were they those of the hyperplastic adrenal cortex in the adreno-genital syndrome. They were much larger than normal and polyhedral in shape, with a smaller, darkly-stained eccentrically-placed nucleus which might be round or oval. The cytoplasm stained faintly eosinophilic with haemalum and eosin and was much more finely foamy than that of the normal cortical cells. The gland was irregularly trabeculated by thin fibrous strands which sometimes expanded into areas of vascular fibrous stroma. The cells closely resembled xanthoma cells. Throughout the cortex, small rather spindle-shaped cholesterol crystal clefts were seen, with related multinucleated giant cells (Fig. 3). The islets of medullary tissue were scattered and compressed, but the cells appeared to be essentially normal. The vascular arrangements of medulla and cortex also appeared normal.

Paraffin sections stained by Mallory's method showed fine collagen fibrils surrounding the great majority of the cells of the cortex. There were scanty areas, usually adjacent to the cortical surface and sometimes wedge-shaped, in which the cells contained fine fuchsinophil granules. These appearances were paralleled in sections stained by Lieb's phosphotungstic-acid haematoxylin. The Prussian blue reaction showed no significant amount of haemosiderin in the adrenal cells, although it was present in scanty amounts in the stroma.

The periodic-acid-Schiff method gave negative results. According to Pearse (1953) this excludes the presence of polysaccharides, mucopolysaccharides, mucoproteins, glycoproteins, the glycolipids and the cerebrosides (e.g., cerasin) and a group of unsaturated lipoids and phospholipids, including lecithin, cephalin, phosphatidyl, serine and sphingomyelin. It is of some importance to be able to exclude these latter lipoid substances because of their association with the lipoid diseases. Pearse points out that in Gaucher's disease the lipoid-containing cells are stained by the periodic-acid-Schiff technique and this we have confirmed.

Frozen sections stained with Sudan IV and Sudan black showed that the cortex contained large quantities of sudanophil material uniformly distributed. This was

FIG. 1.—Macroscopic appearance of a kidney and adrenal to show loss of normal morphology of the latter. × 2·5.

FIG. 2.—The adrenal cortex, showing loss of usual zonal arrangement and the atypical appearance of the cells of the cortex. Haemalum and eosin × 50.

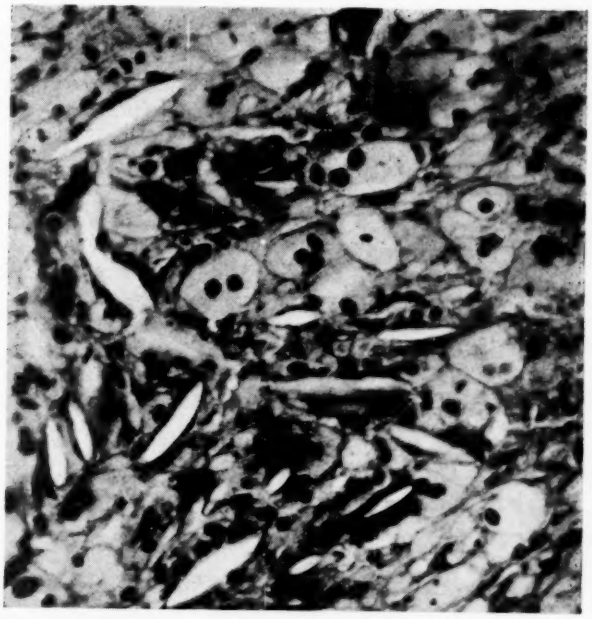

FIG. 3.—An aggregate of cholesterol crystal clefts with foreign-body giant cells. These are surrounded by cortical cells of atypical appearance. Haemalum and eosin × 280.

FIG. 4.—Heterotopic adrenal cortical tissue of similar nature associated with an ovary. Haemalum and eosin × 50.

mainly crystalline, although some droplets were also present. These crystals formed sheaves of slender acicular spicules which were highly refractile in reflected light and brightly anisotropic when examined with polarized light. The large clefts associated with the giant cell reaction did not show birefringence and were not sudanophil and presumably the contained cholesterol crystals must have been dislodged in preparation of the sections.

Two small nodules, 1 mm. in diameter, of heterotopic adrenal cortex, presenting an appearance essentially similar to that of the adrenal cortex, were found close to one ovary, demonstrating that the affection was one of adrenal cortical tissue generally (Fig. 4).

The pituitary showed no gross abnormality. Cell-type differentiation was incomplete.

Discussion

The adrenal glands in this case were obviously grossly abnormal both macroscopically and microscopically. No comparable case is to be found in the records of the Royal Hospital for Sick Children, Glasgow, nor, I am informed, has any such case been previously seen by MacDonald, Cappell or Baar. The condition is not described in the standard works on endocrinology of Grollman (1936), Young (1937), Soffer (1946 and 1951), Hartman and Brownell (1949), Williams (1950) or Yoffey (1952); on paediatrics of Nelson (1950); or on paediatric pathology of Potter (1952) or Morison (1952). No similar case is recorded in the bibliography of the physiology and pathology of the newborn for the period 1930-40 compiled by Antonov (1947) nor is there any relevant reference in the *Cumulative Index Medicus* until 1952.

Thannhauser (1950) chronicles no instance of generalized lipoidosis of the adrenal cortex. He points out, however, that the peri-adventitial cells of the adrenal act as reticulo-endothelial cells and may take up lipoid. Nests of lipoid-containing cells may be discovered in the adrenals in infantile Gaucher's disease and in Niemann-Pick's disease. In both, pigmentation of the skin has been observed. In neither of these diseases, however, is the adrenal ever solely affected. In Gaucher's disease, the spleen, liver, bone marrow and lymph nodes are involved, while in Niemann-Pick's disease the lipoid-containing cells are virtually ubiquitous. In this disease the adrenals may be enlarged and show foam cells localized between cortex and medulla, sometimes causing great thickening of the latter, as the foamy cells are here derived from the reticulum cells of the medulla. In these instances, melanin pigmentation of the skin may be the sole sign of endocrine disturbance. The lipoid-containing cells in Niemann-Pick's disease are isotropic, sudanophil, smaller than those of infantile Gaucher's disease, with rarely more than three nuclei in a cytoplasm which shows small droplets and stains bluish with Mallory's stain. In infantile Gaucher's disease the cells are larger, show many eccentric nuclei in a homogeneous, dense, wax-like cytoplasm which is not sudanophil and stains strongly blue with Mallory's stain. The cells in the present case in no way correspond with those of either condition. In the Hurler-Pfaundler syndrome of gargoylism the cells are not sudanophil and the adrenals are not affected.

Recently the syndrome of neonatal cortical insufficiency has been described by numerous authors, e.g., Butler, Ross and Talbot (1939), Thelander and Cholffin (1941) and Jaudon (1948). This is associated with an adrenogenital syndrome whose histological findings are described by Allibone, Baar and Cant (1947). The adrenal in this syndrome shows no similarity to the condition described above, and in the present case also there was no masculinization or pseudo-hermaphroditism. It seems, therefore, that no relationship exists between the adrenogenital syndrome and the present case.

Stoner, Whiteley and Emery (1953), in a comprehensive and well-illustrated paper on the effect of systemic disease on the adrenal cortex of the child, outline the post-natal development of the adrenals. They state that at birth there is little sudanophil material in the definitive cortex or in the so-called X-zone, and that the lipoid content increases with age.

Hartman and Brownell (1949) state that at birth the cholesterol content of the adrenal is only 15 mg. per g. Ether extracts, on the other hand, contain chiefly glycerol tristearate, and lecithin and cephalin have also been identified. They cite Rosenheim and Tebb to have demonstrated sphingomyelin and Coester cerebroside.

Chemical Analysis

Dr. R. P. Cook, of the Department of Biochemistry, Queen's College, Dundee, kindly made an analysis of a portion of the adrenal from this case and, in comparison, that from a 4-month-old male infant who died of fulminating respiratory infection.

The essential findings are as follows:

	Morbid Adrenal (g.)	Adrenal for Comparison (g.)
Dry weight	0·49	1·01
Lipid extract	0·34 (70%)	0·80 (80%)
Total sterol	0·082 (16·8%)	0·059 (5·9%)
Free sterol	0·026 (5·3%)	0·025 (2·5%)
Ratio total to free sterol	3·3	2·35
Phospholipid	0·021	0·014

Data concerning the lipoid content of the adrenal in childhood and its partition chemically are not readily available. Nevertheless, the figures obtained above show a marked difference in sterol content. There is, of course, a diminution of adrenal lipoid in cases of infection and it is uncertain to what extent this occurs in fulminating disease. Despite the absence of an acceptable control, which would be provided only by a child dying instantaneously for accidental reasons, these figures are published in the hope that data may eventually be accumulated which will give the requisite control values.

Summary

A case of apparent lipoidosis of the adrenal cortex in an infant is described.

This change affected only the adrenal cortex and a portion of heterotopic adrenal cortex associated with one ovary.

The essential change appears to be an increase in cortical sterol with disorganization of the normal zonal architecture of the cortex.

The clinical condition was consistent with adrenal insufficiency.

My thanks are due to Dr. J. H. Hutchison for permission to publish this case, to Messrs. L. Nicolson and W. Mason for technical assistance and to Dr. R. P. Cook and Miss S. K. Bisset for the chemical analyses.

Professor D. F. Cappell and Drs. A. M. MacDonald and H. S. Baar examined the sections and I am grateful to them for advice and encouragement. I am also indebted to Professor M. J. Stewart for much helpful criticism.

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MENTAL RETARDATION, PIGMENTATION OF THE SKIN, XANTHOMATOSIS AND LEUKAEMIA

BY

J. L. EMERY, J. LORBER and J. D. SHEWARD

From the Sheffield Children's Hospital and the University of Sheffield

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The syndrome to be described, namely skin pigmentation followed by xanthomatosis and subsequently myeloid leukaemia, in a mentally retarded child has apparently not been described before.

Case History

G.S., a boy, the third child in a family, was born at term by normal delivery at the Jessop Hospital for Women, Sheffield, on February 9, 1951, after an uncomplicated pregnancy. He weighed 5 lb. 12 oz. No abnormalities were noted at birth, and progress during the neonatal period was uneventful. There was no family history of lipoid storage disease. As the mother suffered from active pulmonary tuberculosis, the infant was separated from her and was vaccinated with B.C.G. This procedure was followed by Mantoux conversion. He was examined at intervals in the tuberculosis contact clinic of the Sheffield Children's Hospital. At the age of 14 weeks he weighed 13 lb. 3 oz. He was well, could smile, could hold objects put into his hand, and was able to lift his head momentarily from the supine position. At the age of 46 weeks he weighed 17 lb. 6 oz. He was quite well, but was considered to be retarded at this stage. He refused to have solid foods. He made no attempt to pull himself into the sitting position, although he could sit without support when he was put there. He would say syllables; he would only occasionally laugh; he had no interest in his toys and he only very occasionally transferred an object from one hand to the other. By now, he was found to have *café-au-lait* spots and he had an enlarged spleen.

At 1 year of age he weighed 17½ lb. He showed no improvement in his mental condition. He was unable to get into the sitting position. He could not crawl and made no attempt to stand. He now rapidly transferred objects from one hand to the other. He could not say a single word. Professor Illingworth considered at this time that he was severely backward with a developmental quotient of approximately 75. The physical signs had not altered. He had no xanthomata.

At 14 months of age he was admitted for investigation. He had suffered from a cough for three weeks before his admission but was not acutely ill. He weighed 16 lb. 1 oz. There was a nasal discharge and scattered rales and rhonchi were heard over both lungs. The spleen was enlarged and firm, reaching three finger-breadths below the costal margin. The liver edge was palpable an inch below the costal margin and small, discrete enlarged lymph nodes were felt in the axillae, groins and neck. Scattered *café-au-lait* patches of pigmentation were seen in the skin, but no other cutaneous abnormalities were found. No other abnormal physical signs were detected.

Haematological findings were as follows: Haemoglobin, 10 g. %; white cell count, 17,400/c.mm. (polymorphs 38%, lymphocytes 48%, eosinophils 2%, monocytes 12%). No primitive cell forms were seen in the peripheral blood. The bone marrow smear showed some depression in erythropoiesis, but no evidence of leukaemia. The cerebrospinal fluid and urine showed no abnormalities. The blood and C.S.F. Wassermann reactions were negative.

After discharge home he remained symptom free, though backwardness persisted. He was about 2 years old when he first walked without assistance, and at this time his speech was still limited to monosyllables.

At the time of his final admission to hospital at 3 years of age, the boy had been ill for about a month. He was not eating well and was noticeably thinner. A loose productive cough had developed with fever, lassitude and general malaise. On admission he looked pale, thin and acutely ill. He had a loose, distressing cough with a mucopurulent nasal discharge and fever. The percussion note was impaired at the apex of the right lung, and there were generalized rales and rhonchi. The abdomen was distended and ascitic. The scrotum and ankles were oedematous. The liver was firm, enlarged and palpable 2 in. below the costal margin. The spleen was palpable 3 in. below the costal margin, and the impression of its lower margin could be seen against the lower abdominal wall. Discrete, enlarged, firm lymph nodes were palpable in the cervical axillary and inguinal regions. Scattered *café-au-lait* patches were still present in large numbers, and some of them were very large. A new feature was xanthomata as bright yellow papules, 0·5 to 1·0 cm. in diameter, sparsely scattered on the chest and abdomen, but more heavily

distributed on the scalp. A typical xanthomatous plaque was also seen on one conjunctival surface. No petechiae were visible at this time. No abnormal signs were found in the central nervous system. The optic fundi were normal. There was no evidence of cardiovascular disease. Mental retardation was still evident, though its exact degree could not be determined because he was now very ill.

During this admission full blood investigations were made and the following results obtained: Haemoglobin, 8·3 g. %; red blood cells, 2,900,000/c.mm.; nucleated red cells, one per 300 leucocytes; platelets, 21,000/c.mm.; total white cell count, 266,000/c.mm. (polymorphs 57%, monocytes 22%, basophils nil, myelocytes 9%, eosinophils nil, lymphocytes 10%, primitive cells 2%). The bleeding time was 8 minutes 45 seconds (Duke's method). The clotting time was 6 minutes (capillary method). Bone marrow smears showed abnormal forms in all the blood elements. The picture was that of chronic myeloid leukaemia. Tubercle bacilli were not demonstrated by appropriate techniques.

An xanthomatous plaque was removed under local anaesthesia and the histological appearances confirmed the presence of xanthoma cells with no evidence of neoplastic infiltration.

Biochemical investigations gave the following results: Total serum lipoids, 483 mg. %; serum cholesterol, 59 mg. %; thymol turbidity, 12 units; zinc sulphate test, 60 units; serum albumin, 2·3 g. %, and serum globulin, 2·4 g. %.

Serum electrophoresis demonstrated increased gamma globulin levels.

Apart from a trace of albumin the urine was normal.

A radiograph of the chest showed a dense opacity in the right upper zone with a convex lower margin (Fig. 1). There was calcification in the axillary lymph nodes on both sides, as a result of the B.C.G. inoculation. The Mantoux reaction, 1 in 1,000, was positive. No significant abnormalities were seen in the radiographs of the skull and long bones.

The respiratory symptoms and chest radiograph led to a diagnosis of an unresolved right upper lobe pneumonia. Following large doses of penicillin, there was some improvement in the child's respiratory distress with a fall in temperature, but his general condition worsened, with increasing pallor, oedema and ascites. Further radiographs of the chest showed no improvement. Later there was a further increase in the respiratory distress accompanied by high fever. Generalized petechial haemorrhages appeared in the skin. His general condition deteriorated and did not respond to courses of soluble penicillin and aureomycin. Further haematological examinations revealed an increasing degree of anaemia, the haemoglobin steadily falling to 4·2 g. %, persistence of the leucocytosis with an eventual rise to 336,000/c.mm. (Fig. 2) and a progressive thrombocytopenia. Urethane, 0·125 g., was given six hourly for several days without effect on the white cell count. He ran a continuous irregular high fever throughout the latter part of his illness, and his condition slowly deteriorated until he died at the age of 3 years and 3 months, 10 weeks after his admission.

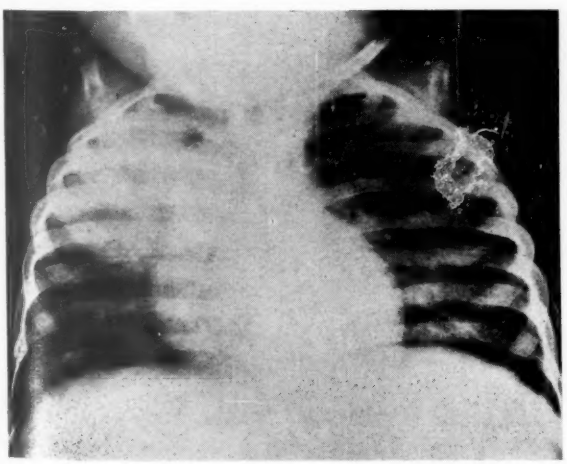

FIG. 1.—Radiograph of chest 10 weeks before death.

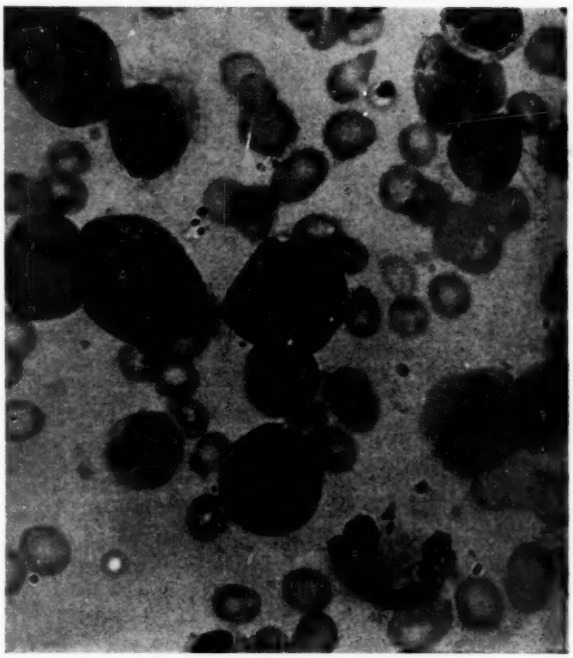

FIG. 2.—Peripheral blood smear showing the leukaemic blood picture.

Necropsy. The body was that of a wasted male child with no anatomical deformities. There was oedema of the feet, lower parts of the legs, sacrum, forearms and hands. The skin showed two distinct lesions. There were large *café-au-lait* patches, particularly on the trunk, of approximately 2 cm. in diameter (Fig. 3), and there was a much larger number of discrete, slightly raised xanthomatous areas—particularly prominent over the scalp and face, and varying from 2 to 8 mm. in diameter.

The peritoneal and pericardial cavities contained sero-

FIG. 3.—Necropsy view of the upper trunk showing the areas of skin pigmentation and the size of the liver and spleen.

sanguinous fluid, and within the serous membrane were a number of almost circular xanthomata (Fig. 4).

The left pleural cavity had firm adhesions and the right was almost completely obliterated except for the mid-lateral third where there was a chronic empyema extending into the intralobular fissure. The respiratory tract contained mucopus and in the lungs there were many areas of consolidation.

The heart muscle was very pale, and xanthomatous areas were present in the connective tissue around the coronary arteries. Similar areas were present in the liver and kidneys.

The intestinal tract showed no abnormality other than a large number of small haemorrhages in and from the mucosa.

The liver was enlarged and weighed 855 g. (normal 400-500 g.). It was pale, with yellow xanthomatous areas around many vessels. The spleen was large and weighed 296 g. (normal 35-40 g.). It was very firm and deep red. The kidneys were pale and not grossly enlarged and weighed 132 g. (normal 90-120 g.). The other viscera showed no gross changes, and the endocrine glands appeared normal. The brain was of normal weight and showed no gross abnormalities, no xanthomata being seen around the superficial vessels.

The lymph nodes in the axilla associated with the B.C.G. inoculation were small and calcified. Throughout the rest of the body the nodes were enlarged, particularly in the mediastinum and mesentery. None showed caseation or necrosis.

Histology. The general architecture of the lymph nodes, the spleen and the bone marrow was almost entirely replaced by diffuse masses of primitive cells. Similar types of cells were present in large infiltrating masses in the kidneys, intestinal mucosa, liver, testes and in a lesser degree in all of the other organs examined with the exception of the thymus and the brain.

The xanthomatous areas were entirely devoid of the leukaemic infiltration, and contained both neutral fats and doubly refractile material, as in the biopsy specimen.

The lung contained many acute abscesses as well as evidence of long-standing infection, and there was considerable alveolar oedema.

An extensive search was made for intranuclear inclusion bodies in the liver, kidney and other organs, but none were found. No abnormality was recognized in the structure of the brain in preparations by routine methods.

Discussion

This child presented when he was a year old with mental retardation, splenomegaly, lymphadenopathy and patchy cutaneous pigmentation. For the next two years his general health was fair, although his mental retardation and splenomegaly persisted. The appearance of scattered cutaneous xanthoma was noted when his health rapidly deteriorated at the age of 3 years. He had extreme leucocytosis and the bone marrow appearances were those of a chronic myeloid leukaemia. Necropsy revealed xanthomatous lesions in the viscera, leukaemia and gross pulmonary infection.

Skin xanthomata occur in a number of diseases in childhood (Crocker, 1951; Freud, 1951; Thannhauser, 1950) and are usually clinically separated into two broad groups, based on the serum cholesterol and fat levels. The group in which the serum cholesterol level is usually normal, as in our case, includes a benign form of cutaneous xanthoma, various chronic diseases especially the 'eosinophilic granuloma syndromes' (Thannhauser, 1950), leukaemia and von Recklinghausen's neurofibromatosis (Crocker, 1951).

Most cases with visceral juvenile xanthoma had a fatal outcome (Thelander, 1949) but Thannhauser (1950) and Crocker (1951) each recorded a child whose general health remained good.

FIG. 4.—Photograph of the upper surface of the liver falciform ligament and diaphragm. There is a round xanthomatous plaque in the ligament and another on the upper surface of the liver.

Mental deterioration occurs in the infantile form of Gaucher's disease and Niemann-Pick's disease, but was not described in the cases of xanthomatosis of Thannhauser (1950) and Crocker (1951). Thelander (1949) reported a child with xanthomata, hepatosplenomegaly and mental retardation, who died after recurrent periods of ill health lasting 20 months. The bone marrow at no time showed evidence of leukaemia and the brain appeared normal as in our case.

The only previous description of a child that corresponds closely to the case reported here is that which Freud and his colleagues reported in a series of four papers (Freud, 1951 and 1952; Freud, Plachta, Speer and Luhby, 1954; Freud and Plachta, 1954). Their child presented with xanthomatous skin lesions. Twenty-five months later the child developed a generalized reticulo-endotheliosis and later developed leukaemia. At necropsy numerous inclusion bodies were found, particularly in the liver. The present case differs principally in the final point, in that after a prolonged search we were unable to find intranuclear inclusions. It was upon the finding of the intranuclear inclusions that it was suggested that the condition may have had an infective origin. If these two cases are in fact similar it would suggest that the presence of intranuclear inclusions in the earlier reported case was fortuitous, and that the disease syndrome is a general non-specific neoplastic disorder of the reticulo-endothelial system.

Summary

A case is reported of a child suffering from a systemic reticulo-endotheliosis, characterized by mental retardation, hepatosplenomegaly, lymphadenopathy and cutaneous xanthoma, who later developed chronic myeloid leukaemia.

We are indebted to Professor R. S. Illingworth for his criticism of this paper.

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A STUDY OF THE ONSET OF RESPIRATION IN THE NEWBORN

BY

J. S. FRASER

From the City Maternity Hospital, Carlisle

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In this study the different types of respiratory onset have been observed at the birth of 190 babies, and as a preliminary a brief review is made of the development of the mechanism for pulmonary respiration and the factors involved in the onset of such respiration.

Development of the Mechanism for Pulmonary Respiration

Barcroft (1946), in a series of experiments on sheep foetuses, observed the physiological development of the foetal nervous system. It starts at the lower part of the medulla, at the thirty-fourth day in the sheep, when the first reflex movements are obtainable. Stimulation of the trigeminal nerve at first causes localized movement of the head, then movements of the rest of the body, including the diaphragm. At the next stage the same stimulation causes a series of 10 to 20 rhythmic spasms involving the whole body. Each spasm resembles a gasp.

Barcroft was able to transect the brain in older foetuses without disturbing their growth *in utero* and by transecting at different levels he identified the parts of the brain involved in the different types of reflex movements.

The second stage of rhythmic spasms was found to involve the upper part of the medulla.

The third stage, one of segregation, develops about the forty-fifth day, when stimulation of the trigeminal nerve caused a movement of the whole body, followed, after a pause, by a respiratory rhythm. At this stage the pons Varolii is functioning.

The foetus becomes increasingly sensitive to stimuli and then, about the sixtieth day, becomes quiet. The stage of inhibition has developed and a sharp stimulus is necessary to produce any reflex movement. It involves the functional development of the inferior corpora quadrigemina.

The nervous mechanism for pulmonary respiration is now completed but, as the halfway period of gestation has not been reached, it will be seen that the mechanism is ready long before it is required, and it is known that this mechanism even functions before birth, for Davis and Potter (1946) have shown that the foetus 'inspires' amniotic fluid.

Factors in the Onset of Respiration

The onset of respiration is believed to be caused by chemical rather than physical factors.

Immediately after birth the placental circulation is markedly impaired by the contracting and retracting uterus. This results in a diminution of the oxygen supply to the foetus and an increase in the carbon dioxide tension in the blood stimulating the respiratory centre to action. Schmidt (quoted by Smith, 1945) has shown that although the respiratory centre in the medulla is normally sensitive to changes in carbon dioxide tension in the blood, the chemoreceptors in the aortic and carotid bodies are particularly sensitive to oxygen lack and reflexly stimulate the respiratory centre.

Where anoxia is too great, the respiratory centre, together with the aortic and carotid bodies, becomes paralysed and the onset of respiration fails to take place. Heavy sedation also has a depressant action.

Types of Onset of Respiration

This study of the onset of respiration in the newborn was undertaken to determine the type of onset which occurred most commonly and four series of cases were observed.

(1) Spontaneous deliveries	125 cases
(2) Forceps deliveries	35 cases
(3) Caesarean section deliveries ..	20 cases
(4) Breech deliveries	10 cases

As will be seen from Table 1, the gasp, or short inspiratory respiration, was the most frequent type of onset in all modes of delivery. This included all cases where the gasp was distinct, although followed almost immediately in some cases by the onset of continuous respiration. Also included in this group were those cases where the onset was a cry, because,

although the predominant part of the breath was expiratory, there was a preliminary short inspiration.

According to Barcroft the gasp indicates that only the lower part of the medulla is functioning, the inference being that the centres higher up have been rendered functionless, probably by anoxaemia. These parts of the brain, having started functioning later than the medulla, are affected earlier.

TABLE 1
TYPE OF ONSET IN FOUR MODES OF DELIVERY

Type of Onset	Spontaneous Births	Forceps Births	Caesarean Sections	Breech Births	Total
Gasp	109	34	16	10	169
Rhythmic gasps with general body movements ..	4	0	1	0	5
Rhythmic gasps alone	12	1	3	0	16
Normal quiet respiration ..	0	0	0	0	0
Total in series ..	125	35	20	10	190

The second type of onset was seen in very few cases. Here a regular series of gasps occurred, associated with movements of other muscles, usually of the head and neck alone, but occasionally of the limbs also. According to Barcroft, the higher parts of the medulla were thus functioning.

In a slightly larger number of cases a series of gasps occurred without other muscular movement. This was the third type of onset and indicated that the eighth nerve nucleus was functioning.

No cases were seen where normal quiet respiration occurred from the onset. This meant that the centres above the pons were not functioning. It will therefore be seen that in all the cases studied, a degree of anoxaemia was present, extending to various levels in the brain.

Barcroft suggested two methods of inducing the onset of respiration. First, by the weakening of the inhibitory control originating above the pons, and, secondly, by increasing the bombardment of sensory impulses upon the lower centres so that they overcome the inhibition. In all cases studied, therefore, the onset of respiration occurred following the weakening of the inhibitory control due to anoxaemia.

Barcroft described one case where the onset of respiration was a single prolonged respiration, and suggested that this was an intermediate type. There was however, no case in this series where the inspiration was prolonged and could be termed anything more than a gasp.

Delay in Onset of Respiration

The periods of apnoea preceding the onset of the first respiration and the onset of continuous respiration were also observed and are noted in Tables 2 and 3.

TABLE 2
TIME BEFORE THE ONSET OF FIRST RESPIRATION

Onset of First Respiration	Spontaneous Births	Forceps Births	Caesarean Sections	Breech Births	Total
Within 5 seconds ..	94	2	3	0	99
Within 1 minute ..	27	14	13	8	62
Within 2 minutes ..	4	10	0	0	14
Within 5 minutes ..	0	8	2	2	12
Within 8½ minutes ..	0	1	2	0	3
Total in series ..	125	35	20	10	190

TABLE 3
TIME BEFORE THE ONSET OF CONTINUOUS RESPIRATION

Onset of Continuous Respiration	Spontaneous Births	Forceps Births	Caesarean Sections	Breech Births	Total
Within 5 seconds ..	53	0	0	0	53
Within 5 minutes ..	65	31	10	9	115
Within 10 minutes ..	7	4	10	1	22
Total in Series ..	125	35	20	10	190

As would be expected, the onset of the first respiration was delayed in the abnormal types of delivery. This was particularly the case in the forceps deliveries, where compression of the head by the forceps blades and cerebral oedema and haemorrhage cause further anoxaemia of the respiratory centres.

A certain degree of anoxaemia, however, is necessary to overcome the inhibitory control of respiration. This anoxaemia takes longer to develop in cases of Caesarean section where delivery is rapid and this explains the high proportion (50 %) of cases where the onset of continuous respiration was delayed for more than five minutes.

Summary

The onset of respiration was observed in 190 cases comprising four series, namely spontaneous, forceps, Caesarean and breech deliveries.

The gasp, or lower medullary type, most frequently initiated respiration in all groups.

In no case did the onset occur with normal respiration, indicating that some degree of anoxaemia was present in all cases.

The periods of apnoea before the onset of respiration were noted. The longer periods of apnoea occurred mainly following abnormal types of delivery, due probably to superadded cerebral oedema and haemorrhage.

I wish to thank Professor Kellar who suggested this study and in whose unit in the Simpson Memorial Maternity Pavilion the deliveries took place.

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BOOK REVIEWS

Diseases of Infancy and Childhood, 7th ed. By WILFRED SHELDON. (Pp. xii + 804; 213 figures. 50s.) London: J. A. Churchill. 1955.

This book on paediatrics, something, as the author claimed in its first edition, more than a mere handbook, retains its popularity and appears once again, only slightly swollen and still vested with a characteristic modesty which, while it enhances the distinction of the writing, scarcely conceals a disregard for modern trends in textbook production.

The claims of advancing medicine are adequately met by a dozen or more descriptions of conditions that were not known or recognized previously and by considerable re-writing of sections dealing with such conditions as prematurity and vitamin-resistant rickets, about which our knowledge has grown and changed; also by a lurid coloured frontispiece. Links with the past include 10 pages on diphtheria, some charming footnotes on such themes as how to make liver broth (p. 588) or hydrochloric acid milk (p. 694), and a harrowing description of how to resuscitate an infant with gastro-enteritis on the verge of collapse by holding it in a mustard bath until the nurse's arms tingle.

Dr. Sheldon's book will, and certainly deserves to, retain its popularity. It is simply written, easily handled, deceptively full of useful information and deals with all the common conditions and many of the rarities of modern paediatrics. It has, moreover, that mysterious quality that makes even Dr. Sheldon's paediatric colleagues reach for it on a shelf where it sits proud and aloof amongst its multivolumed continental and transatlantic competitors.

Handbook of Paediatrics. By H. K. SILVER, C. H. KEMPE and H. B. BRUYN. (Pp. 548; 31 chapters; illustrated. $3.00.) Los Altos, California: Lange Medical Publications. 1955.

This pocket-sized textbook of paediatrics defies description. Weighing a few ounces and measuring 7 in. × 4 in. × 1 in. it sits easily and unnoticed in the coat pocket. Yet its 550 pages embrace the whole of paediatrics. The subject matter is concise and highly systematized, with headings and sub-headings in descending order, whilst a vast amount of accurate information is conveyed by a multitude of plans, illustrations, charts, tables and schemata.

All the major diseases of childhood are adequately dealt with, and information on recently described conditions, new forms of therapy and modern concepts of physiology and pathology is up to date. Normal physiological and psychological development is taken from puberty through to adolescence. Anthropometric and physiological data, a drug index, poisons and antidotes chart and conversion tables completes the picture.

The semi-stiff binding is adequate, the paper is tissue thin, and the printing is outstanding for its clarity and beauty.

On the shelf beside a multivolumed system of paediatrics one is reminded of Jack the Giant Killer.

Amazing value for 3 dollars.

The Medical Annual. Edited by SIR HENRY TIDY and PROFESSOR R. MILNES WALKER. (Pp. xliv + 548; 63 plates. No price given.) Bristol: John Wright. 1955.

This, the 73rd edition of the *Medical Annual*, follows the tradition and format of its immediate forerunners and, as usual, affords an admirable bird's eye view of the previous year's outstanding work. The eminence of the contributors ensures that the year's advances are dealt with in an authoritative manner, and the volume will be as useful to the specialist wanting to know what his colleagues in other specialties have been up to as to the family doctor attempting to keep up with the whole of medicine. Few will read all 548 pages, but everyone will find something in the Annual to interest and inform them.

Problèmes Néo-Nataux. Conférence d'Actualités Pratiques. Faculty of Medicine, Paris. By M. LELONG, F. ALISON, R. LAUMONIER, A. ROSSIER, R. JOSEPH, S. BUHOT, F. LEPAGE and J. BERNARD. (Pp. 86; 4 figures. Fr. frs. 420.–) Paris: Masson. 1955.

'En imprimants ces textes, nous avons pensé être utiles à ceux des auditeurs qui, pour mieux en pénétrer le sens, desiraient lire, à tête reposée, dans le silence du cabinet, une conférence précédement entendue.'

These words, conjuring up what vision of education through 'sessions of sweet silent thought', introduces the new series of conferences on neonatal problems from the Medical Faculty of the University of Paris. The postgraduate seminar or round table conference, slow to enter English medical education, has considerable advantages in disseminating knowledge, and this collection addressed to obstetric, paediatric and postgraduate students covers the subjects of infant mortality, neonatal trauma, necropsies on premature infants, treatment of white asphyxia, neonatal infection, early diagnosis of oesophageal atresia and haemolytic disease of the newborn. These chosen subjects are covered adequately

but simply; addressed, perhaps, more to the future obstetrician than to the budding paediatric consultant.

Many of the vital neonatal statistics (Marcelle Lelong) and figures of foetal deaths (R. Laumonier) make useful comparison with our more familiar English figures, and the plea for the earliest diagnosis of oesophageal atresia (Marcelle Lelong) is worth reading if only for its presentation and style. Briefly, Dr. Lelong says that early diagnosis is so vital that the obstetricians or midwife's bag is incomplete without an oesophageal sound which should invariably be used on the occurrence of any one of the easily recognizable symptoms.

A reliance on caffeine, as the drug *le plus efficace et le moins nocive* (surely quite incompatible opposites) in the treatment of white asphyxia (A. Rossier) sounds anachronistic to English ears, and the prophylaxis of maternity hospital and neonatal infection (R. Joseph) by complete asepsis is a method of avoiding rather than facing the essential issue, the wickedness, as it were, of this bacteria-ridden world. A good third of the book is occupied by a review of haemolytic disease of the newborn (S. Bohut, F. Lepage and J. Bernard) which, though necessarily brief, is easy to understand.

For anyone approaching D.C.H., wishing simultaneously to air his French and revise his knowledge of neonatal paediatrics, this volume makes easy and pleasant reading. The book, though paper backed, is well got up, and the printing unusually good.

La Carence de Soins Maternels. By JENNY AUBRY. (Pp. 188. Fr. frs. 720.) Paris: Presses Universitaires de France. 1955.

This account of the effects of 'maternal deprivation', as we now call it, on French babies and young children is the result of observations by a group of 16 people working under the direction of Dr. Aubry. The subject has now worried many of us for some years and in spite of various excellent publications, including the pioneer works of Dr. John Bowlby, we wait to remain completely convinced of the very severe effects which these separations may cause. We look to serious workers in the field to do this.

Dr. Aubry's methods of assessing the degree of interference with the normal and happy development of the children are open to much criticism (the Gesell test, the Wetzel Grid, the assessment of 'health' are indeed controversial matters in themselves), and there is a lack of control figures, while subjective impressions abound. No references are given. It has been said by journalists that it is necessary to 'personalize' science to make a point clear in some forms of writing, and while quoting of particular case histories is admirable in many publications, here we find dramatic accounts of Bernard, Christine and Paul which are clearly intended to shock and sadden us.

This kind of publication does harm to the cause. The plan of research set out to show the effects and dangers of separation from the mother, and it is clear that much work went into the accumulation of results. Unhappily the short monograph has fallen between those two stools which always produce such an irritating result: concise scientific presentation of facts, and scientific discussion heavily biased by subjective ideas and the (sometimes admirable) desire to push over the point. When such a subject is so fraught with difficulty of investigation it is a great pity that such a method of presentation was chosen.

Work in this field has certainly done one great service, namely, to stimulate us to be anxious about the care of children in hospital, and for institutions to think hard about the possible psychological dangers risked. This book ends with an excellent constructive criticism of the present situation in France; it suggests ways of avoiding the possible dangers for children actually in such situations; and, finally, makes a moving plea for more work and interest in the field.

Babies and Young Children. By RONALD S. ILLINGWORTH and CYNTHIA ILLINGWORTH. (Pp. vii + 360; 50 figures and 24 plates. 18s.) London: J. & A. Churchill. 1954.

Two paediatricians who have become parents have formidable authority for writing of their experiences, and it was to be expected that these authors would add to the massive library of advice that already exists to help parents with the upbringing of their children.

The advice given in this book has been thoughtfully pondered and given with due gravity. There are particularly excellent chapters on the pattern of development and the behaviour difficulties of childhood, which between them occupy most of the book.

The writing is straightforward and simple with only occasional difficult passages, though few intelligent mothers would have the patience to unravel the instructions on 'How to Work Out the Quantity' on pp. 78 and 79, which together with the relevant Tables 4 to 6 will surely need recasting. The illustrative sketches are apt and diverting, and the photographs, many by Professor Illingworth himself, are magnificent, and redeem the book of its lack of humour. Where the text drives home its points with almost deadening reiteration, the photographs, technically of professional quality, catch moments of childhood aggression, pathos and charm with sensibility and streaks of sardonic humour.

Parents will work their way through this book, and be greatly helped in their task.

Pre-School Child Mortality in the Netherlands. By H. H. VAN GELDEREN. Translated by P. Vuysje and W. Mulhall Corbet. (P. viii + 138; 55 tables and 22 figures. Florins 9.–) Leiden: Stenfert Kroese. 1955.

This is a very good general and statistical survey of pre-school mortality. It is full of clear and concise statement, together with carefully checked data. The author has gone back a long way so that he may see true trends and comparative mortality rates, and he indicates that the decline in pre-school child mortality has been achieved much more by the relatively slow progress of increasing social consciousness and improvement in social conditions than by the apparently more spectacular results of curative medicine. In this respect he

believes that child mortality can be a sensitive indication of health conditions, especially to the social and economic backgrounds. The overall picture may give the impression 'that a dream of social paediatrics is being realized'.

The reductions of the male birth surplus by neonatal death are gradually being countered and the effects also in the pre-school age group are such as will enable the male surplus to change only a little. From 1 to 4 years of age the child's chance of dying becomes less as his age increases. However, the death rate of the 1 to 4-year-olds is still as high as that of the 35 to 40-year-olds. The higher mortality due to accidents is the main cause of the persistence of an excess mortality of boys.

Seasonal factors in the mortality are evident. In general, winter adds to the stresses and strains. The complex factors causing decline of mortality has a greater effect in summer. There is a slightly higher mortality rate in rural areas than in towns. Some emphasis is laid upon the state of health of the child before the fatal illness as a significant determinant of the end. This was especially noted in undeveloped areas.

In the figures given, the remarkably favourable trend in tuberculosis is clear, but the sad story concerning violent death, especially since 1950, is related. By comparison, Canada seems a dangerous place for pre-school children (50 deaths per 100,000), in the Netherlands 45, and in England and Wales 24; in 1950 in West Germany 59, in Norway 52, in Australia 38, in France 33, in U.S.A. 38. The situation is, therefore, fairly general in its contribution to pre-school deaths.

The author draws a conclusion that the mortality due to road accidents in pre-school children proves to be not directly dependent on the intensity of traffic, but rather on the care and supervision in the family and in general on the related social and hygienic conditions. Deaths from poisoning add to the violent deaths in similar manner. Accident-proneness is considered in relation to the possibilities of the child's individual psychic structure; but little is really known about this. It does suggest any campaign against accidents is of a medical character.

Mortality from tumours remains steady, but there is a slightly increasing figure for the reticuloses.

It is noted that Holland is still troubled with fatal diphtheria in the pre-school age group. Child mortality (age 1-4) in the period 1900-50 fell by 90% in Netherlands, 92% in Sweden, 93% in England, 85% in France. In other words, the author would have us note that the pre-school age mortality is an even more sensitive criterion of social and hygienic conditions than the infant mortality, and that this decline started earlier than the fall in infant mortality and that the pre-school age mortality showed higher peaks during the war years.

Dr. van Gelderen is optimistic: the expectation is warranted that within 15 years the pre-school mortality will decrease to less than 1 per 1,000, or nearly half the present. Then, he states, accidents, congenital defects, neoplasms and reticuloses will account for 75%. Perhaps new discoveries and a betterment of the accident rate will even improve upon this hopeful expectation.

This volume is very readable and has a comprehensive bibliography.

Perinatal Mortality in New York City. Analysed and reported by S. G. KOHL. (Pp. xiii + 112. 20s.) London: Oxford University Press. 1955.

This is a report, published by the Commonwealth Fund, of an important investigation of nearly a thousand 'perinatal' deaths by a sub-committee of the committee on public health relations of the New York Academy of Medicine. The study, which began in 1950, has produced a large number of interesting figures which have been analysed and commented on by Dr. Schuyler G. Kohl. The most arresting findings are that 35% of the deaths were considered to be preventable and that 40% of the deaths associated with Caesarean section could have been prevented by wiser use of the procedure. The more experienced the medical officer in charge and the better the general quality of the hospital work the less were the number of preventable deaths. Paediatricians, obstetricians and midwives will find much in this book to encourage them to better work.

Viral and Rickettsial Diseases of the Skin, Eye and Mucous Membranes of Man. By Harvey BLANK and GEOFFREY RAKE. (Pp. xi + 285. 36 full colour illustrations, 63 black-and-white. 60s.) London: J. & A. Churchill. 1955.

This work covers a field in which there has not been any adequate previous attempt at complete summation of the available mass of published material. The authors have drawn on world sources, published up to and including 1954, as well as on their own considerable experience, and critically review the knowledge available on each disease entity. The introductory chapters on the nature of viruses and rickettsiae and on the diagnosis of diseases caused by these agents are full and instructive, though necessarily greatly condensed. Though no details of technique are given in a book which aims to instruct the clinician rather than the practising virologist, the tables of the methods for investigation of suspected virus infections in general and of each infection in particular are both clear and comprehensive. The mass of the book naturally is devoted to the clinical picture of the diseases affecting the skin and mucous membranes, and in every case theory and fact regarding the pathology and the treatment are critically and objectively examined. Where doubts exist the authors present all the generally accepted data, merely adding their considered personal opinions, and their presentation of the methods of therapy openly reflects the non-specific ways which must, for the moment, be followed by the clinician.

The text is beautifully illustrated, in colour wherever beneficial, and the style is pleasant and most readable. Folklore and literary illusions lighten the chapters and save the text from being a clear but dull scientific presentation of fact. The work must be a useful addition to the shelves and desks of all who deal with the virus and rickettsial diseases of the skin, eye and mucous membranes of man.

Proceedings of the Third Medical Conference of Muscular Dystrophy Associations of America, Inc., New York, October 8 and 9, 1954. (Pp. 324; illustrated.) Published by American Journal of Physical Medicine, New York.

The very American phenomenon of incorporated associations for the study of particular diseases is strange to us in this country, though its beginnings can be seen in parent associations for various handicapping conditions that are growing both in activity and influence.

The Third Medical Conference of the Muscular Dystrophy Associations of America, Inc., met in New York in October, 1954, and was treated to six symposia, four on the biochemistry and physiology of muscle and two dealing with the clinical and social aspects of the dystrophy problem—altogether some 38 papers and discussions which, previously published in the *American Journal of Physical Medicine* (vol. 35, February, 1955), are now collected into this impressive volume.

The papers are all of high standard, making, some of them, original contributions to the understanding of the physiology and biochemistry of muscle contraction, though some appear to be only remotely related to the main subject. To the clinician undoubtedly the most interesting papers are those dealing with the psychological and the social aspects of a steadily progressive condition such as muscular dystrophy. The special needs of such children, particularly in the realm of medical care, housing and schooling are not always recognized, and it is sometimes still difficult to persuade public authorities to accept any particular obligations towards them. There are, also, many questions of management and of psychological adjustment by both patient and parents, which can best be solved by group discussions. The banding together of parents, doctors, research and social workers undoubtedly not only fosters research into the disease but results in improved facilities for the proper care and education these children so badly need. The only doubt that arises lies in the contemplation of the competing interests of a multitude of associations for various handicaps, each committed to the interests of its own particular association.

Hearing Therapy for Children. By ALICE STRENG, WARING J. FITCH, LEROY D. HEDGECOCK, JAMES W. PHILLIPS and JAMES A. CARRELL. (Pp. 371; illustrated. $6.75.) New York: Grune & Stratton. 1955.

This volume gives a full account of the problems of the deaf child. It is largely devoted to the investigation and management of the child for whom little can be done by medical or surgical intervention. There is, however, a short chapter on the conductive type of deafness, and remedial measures are outlined. Audiometry and its technique are described in detail. The methods of education of the deaf child are very fully covered.

Audiometric technicians and established teachers of the deaf will find the work most valuable. It will also appeal to paediatricians and otologists who have the responsibility of directing the education of the child handicapped by deafness.

Diseases of the Ear, Nose and Throat in Children. By T. G. WILSON. (Pp. xii + 307; 145 figures. 70s.) London: William Heinemann. 1955.

This book confines its range specifically to the otolaryngological disorders of childhood. Much of the subject matter in some of these sections is devoted to anatomy, physiology, and function, and differs little from that already covered in standard textbooks; but throughout, the emphasis is upon the points of interest as regards the child, and the difference from adult anatomy and physiology. Congenital abnormalities are fully covered, and the inflammatory states are described with textbook completeness.

There is a chapter on the training and education of deaf children, and on speech defects. Each chapter is concluded by an extensive list of references. The work is beautifully produced with photographs and diagrams.

The author has written a book which will undoubtedly be of value to the general practitioner and the paediatrician. The otolaryngologist and paediatric surgeon will find it a useful sourse of reference.

The Importance of Physiotherapy in the Treatment of Sick Children. By J. M. JEWRY-HARBERT. (Pp. 84; illustrated. 10s. 6d.) London: Staples Press. 1955.

Physiotherapy in the treatment of sick children is a subject which is but little taught in the majority of training courses for physiotherapists, and in staffing a children's hospital it has been found that most of the new staff require some months of training in this specialized branch of physiotherapy after appointment before being able to treat the patients competently. Strenuous efforts have so far failed to persuade the Chartered Society of Physiotherapists to include a period of training at a children's hospital in their training courses, with appropriate examination questions thereon.

To make up for this lack of training of physiotherapists, Mrs. Jewry-Harbert, a former charge physiotherapist at Tadworth Court, the country branch of The Hospital for Sick Children, Great Ormond Street, has written this little handbook. It is a most valuable work for physiotherapists, particularly in the clear way the author describes the physiotherapist's approach to the sick child and in the details of the techniques, especially those of the baby exercises used at Great Ormond Street. There are one or two minor technical inaccuracies on the medical side; for example, she states (*a*) that the Denis Browne talipes splints are padded whereas it is the foot which has the pads stuck on to it, and (*b*) that the splints are applied with a flannel bandage, whereas sticking plaster is used from the beginning—but it is felt that these are relatively unimportant as regards the main purpose of the book.

For physiotherapists who have not had training in children's work this handbook should meet a real need.

BOOKS RECEIVED DURING THE YEAR 1955

(Review in a later issue is not precluded by notice here of books received.)

Family Diet and Health in Pre-War Britain: A Dietary and Clinical Survey. Preface by LORD WOOLTON, Introduction by LORD BOYD ORR. Report to the Carnegie U.K. Trust from the Rowett Research Institute, Bucksburn, Aberdeenshire. (Pp. 164; 9 figures, 45 tables. No price given.) 1955.

The Lung. Clinical Physiology and Pulmonary Function Tests. By JULIUS H. COMROE, JR., ROBERT E. FORSTER, II, ARTHUR B. DUBOIS, WILLIAM A. BRISCOE and ELIZABETH CARLSEN. (Pp. viii + 219; 57 figures. 40s.; $5.50.) Chicago: The Year Book Publishers. 1955.

Remedial Exercises for Postural Defects. Compiled by L. S. ROLLESTON, revised by T. PRICE. (Pp. 16; 16 figures. 2s. 6d.) Bristol: John Wright. 1955.

Psychopathology and Education of the Brain-Injured Child. Vol. II: Progress in Theory and Clinic. By ALFRED A. STRAUSS and NEWELL C. KEPHART. (Pp. x + 266; 37 figures. $6.00.) New York: Grune & Stratton. 1955.

The Pathogenesis of Poliomyelitis. By HAROLD K. FABER. (Pp. xvi + 157; 16 figures. 36s.) Oxford: Blackwell Scientific Publications. 1955.

V[a] Jornadas Argentinas de Pediatría. (Pp. 436. No price given.) Santa Fe—Mayo: Sociedad Argentina de Pediatría. 1954.

Obese Children. By Flemming Quaade. (Pp. 302. No price given.) Copenhagen: printed by Danish Science Press. 1955.

Radiographic Atlas of Skeletal Development of the Knee. By S. IDELL PYLE and NORMAND L. HOERR. (Pp. viii + 82; 29 plates. 31s.) Oxford: Blackwell Scientific Publications. 1955.

Pädiatrischer Röntgenatlas. By M. A. LASSRICH, R. PRÉVÔT and K. H. SCHAFER. Edited by K. H. Schafer. (Pp. xii + 333; 700 figures. DM. 115.) Stuttgart: Georg Thieme Verlag. 1955.

Growth at Adolescence. By J. M. TANNER. (Pp. xii + 212; 57 figures, 10 plates. 32s. 6d.) Oxford: Blackwell Scientific Publications. 1955.

The Care of Young Babies. By JOHN GIBBINS; Foreword by Sir Robert Hutchison. (Pp. v + 212; illustrated. 6s.) London: J. & A. Churchill. 1955.

Diagnosis of Congenital Heart Disease. By SVEN R. KJELLBERG, EDGAR MANNHEIMER, ULF RUDHE and BENGT JONSSON. (Pp. xv + 649; 581 figures. 165s.) Chicago: The Year Book Publishers; distributed in the U.K. by Interscience Publishers. 1955.

Biologische Daten für den Kinderarzt, 2nd ed., Vols. 1 and 2. Edited by JOACHIM BROCK. (Pp. xix + 651 and xxxii + 1183; 78 figures and 177 figures, respectively. DM. 73.– and DM. 125.–) Berlin: Springer-Verlag. 1954.

The Pediatric Years. By LOUIS SPEKTER. (xxv + 734; 21 figures. 90s.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1955.

VIII International Congress of Paediatrics

The Congress will be held in Copenhagen from Sunday, July 22, to Friday, July 27, 1956.

The scientific programme comprises plenary sessions, round-table conferences, sectional meetings, and an exhibition. At the plenary sessions the following lectures will be held:

Monday, July 23

I. *Prenatal Injuries and Malformations*
   1. Genetic injuries from irradiation (atomic bomb)
   2. Prenatal infections
   3. Prenatal prophylaxis

II. *Chemical Agents*
   1. Fluoridated water in the prevention of dental caries
   2. Dangers involved in the use of antibiotics
   3. Dangers from industrially manufactured foods

Tuesday, July 24

I. *Pathology of the Newborn: Anoxia*
   1. Mechanism of anoxia
   2. Pathological anatomy of anoxia.
   3. Oxygen therapy—value and risks

II. *Surgery*
   1. Malignant diseases in childhood
   2. Urological problems
   3. Late results of operation for cyanotic heart diseases

Wednesday, July 25

I. *Child Psychiatry*
   1. Neuroses in childhood
   2. Prevention of accidents
   3. Early diagnosis of mental deficiency

II. *Neurology*
   1. Hydrocephalus
   2. Cerebral palsy—results of long-term physiotherapy
   3. Kernicterus

Thursday, July 26

I. *Infections*
   1. Vaccination against poliomyelitis

II. *Allergy*
   1. Bacterial allergy: diagnosis and incidence
   2. Bacterial allergy: treatment and results

Friday, July 27

I. *Problems in Tropical Paediatrics*
   1. Kwashiorkor
   2. Chagas' disease
   3. Ascariasis

II. *Tuberculosis*
   1. Prophylaxis of tuberculosis
   2. Treatment of primary tuberculosis
   3. Treatment of tuberculous meningitis

Proffered papers will be read in sectional meetings.

It is also planned to arrange round-table conferences with the following subjects: (1) Auricular septal defect, (2) epilepsy, (3) leukaemia, (4) haemophilia, (5) amino-acid metabolism, (6) nephrosis, (7) water and electrolyte metabolism in dehydration, (8) the adreno-genital syndrome.

Films of paediatric interest will be shown in the Congress cinema.

For further information, please apply to:

VIII International Congress of Paediatrics, Domus Medica, 12A Kristianiagade, Copenhagen Ø, Denmark.

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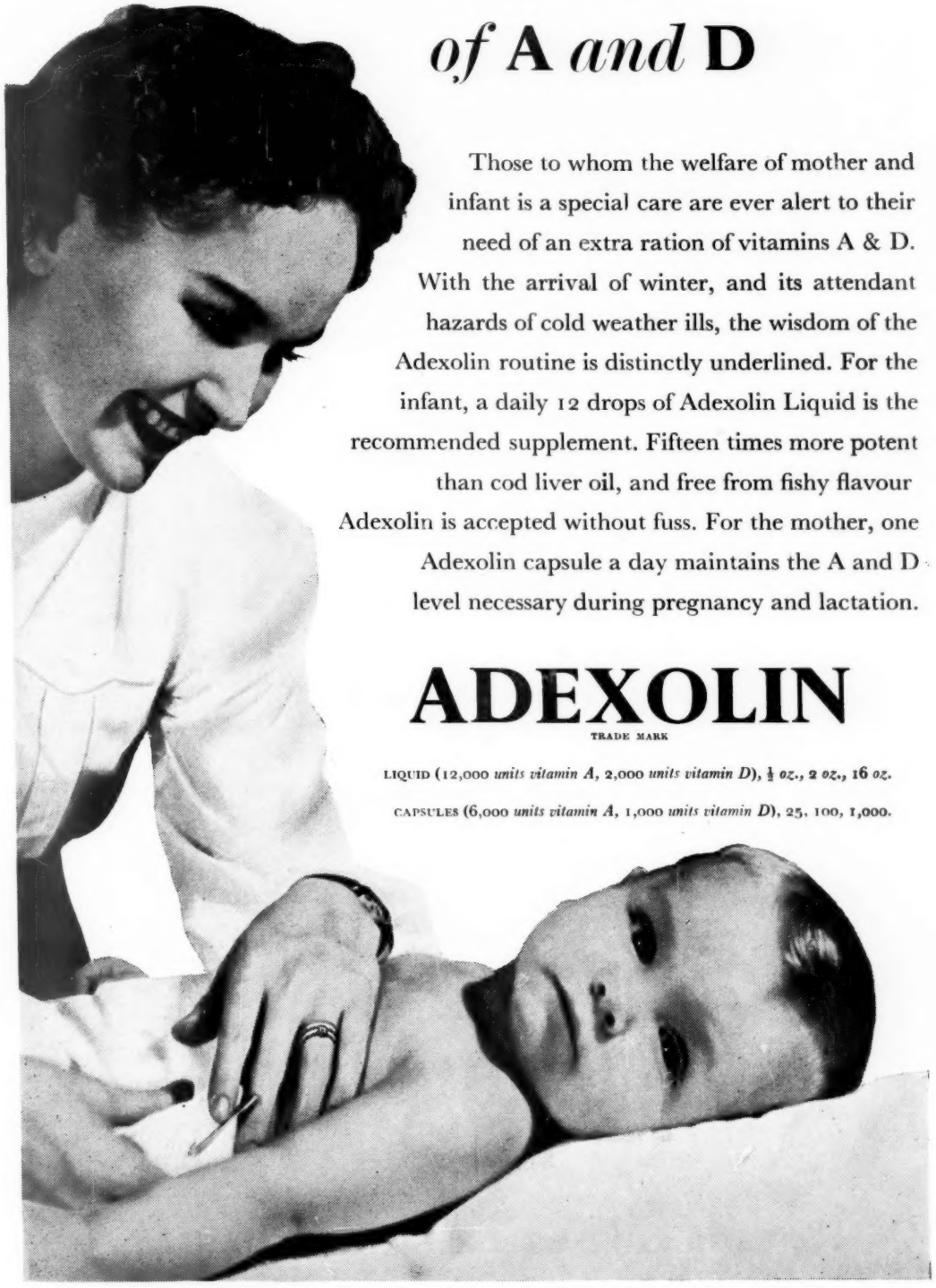

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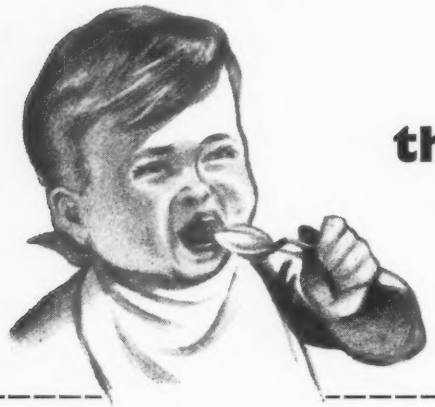

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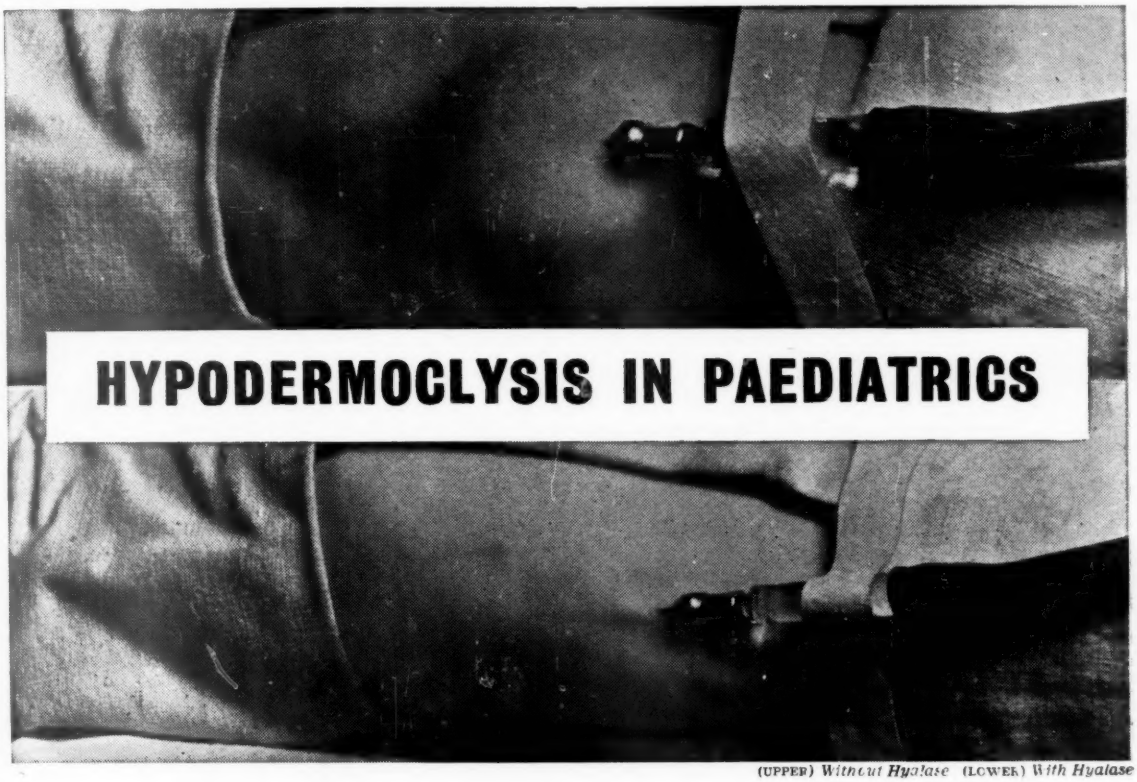

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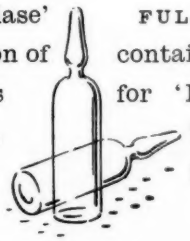

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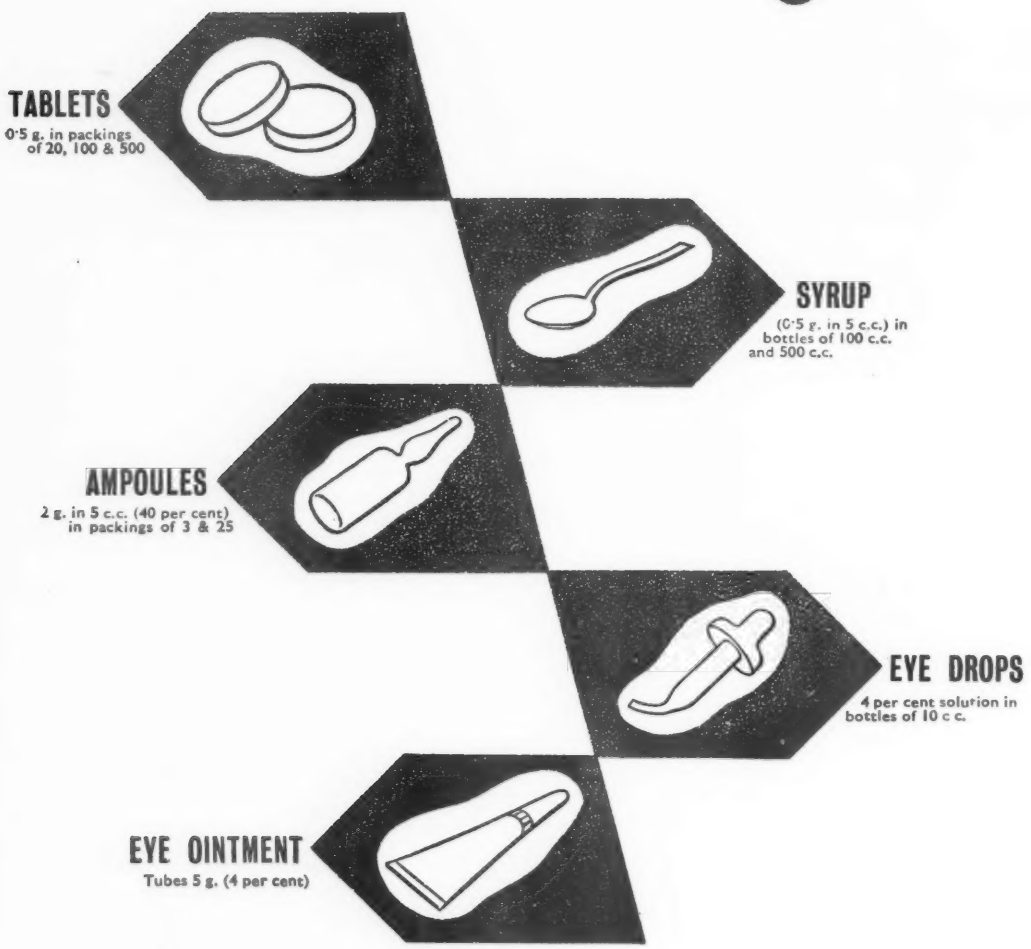
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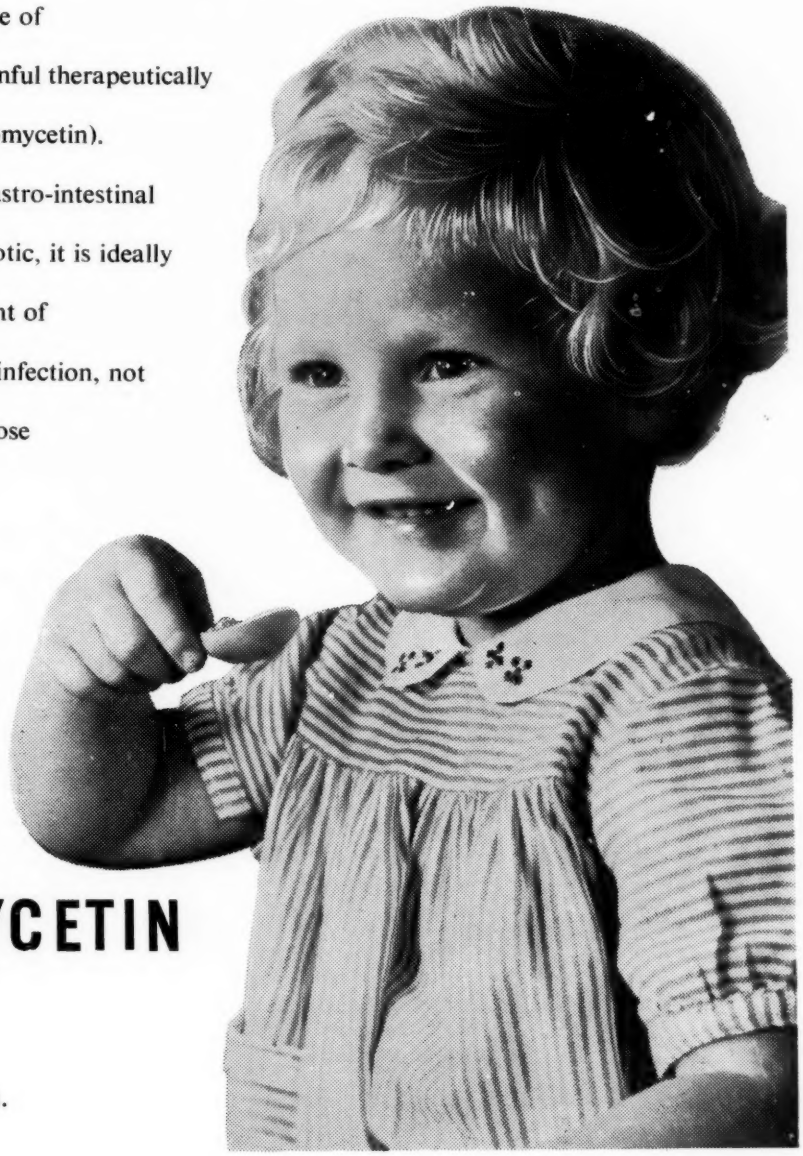

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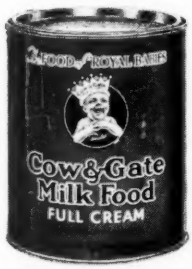

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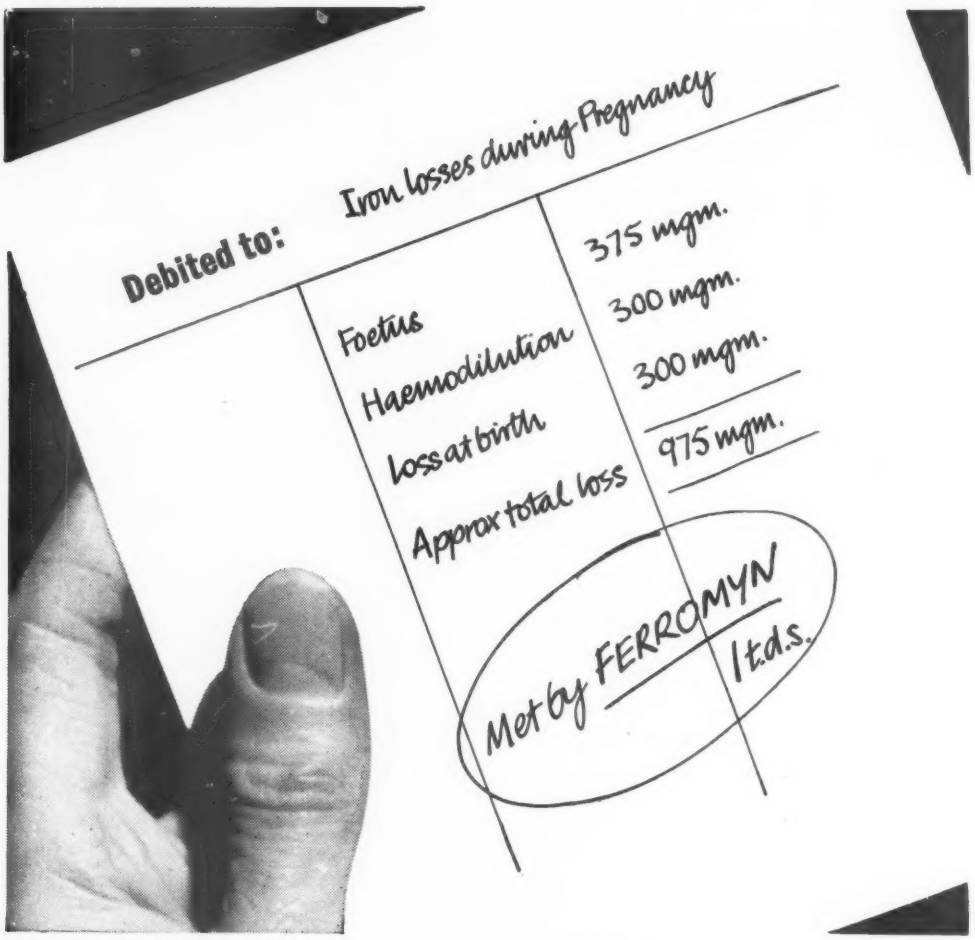

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